

Demonstrating Bioequivalence of Locally Acting Orally Inhaled Drug Products (OIPs): Workshop Summary Report

Wallace P. Adams, R.Ph., Ph.D.,¹ Richard C. Ahrens, M.D.,² Mei-Ling Chen, Ph.D.,³
 David Christopher, M.S.,⁴ Badrul A. Chowdhury, M.D., Ph.D.,³ Dale P. Conner, Pharm.D.,¹
 Richard Dalby, Ph.D.,⁵ Kevin Fitzgerald, R.Ph.,⁶ Leslie Hendeles, Pharm.D.,⁷ Anthony J. Hickey, Ph.D.,⁸
 Günther Hochhaus, Ph.D.,⁹ Beth L. Laube, Ph.D.,¹⁰ Paul Lucas, Ph.D.,¹¹ Sau L. Lee, Ph.D.,¹
 Svetlana Lyapustina, Ph.D.,¹² Bing Li, Ph.D.,¹ Dennis O'Connor, B.S.,¹³ Neil Parikh, B.Pharm.,¹⁴
 David A. Parkins, Ph.D.,¹⁵ Prasad Peri, Ph.D.,³ Gary R. Pitcairn, Ph.D.,¹⁶ Michael Riebe, Ph.D.,¹⁷
 Partha Roy, Ph.D.,³ Tushar Shah, M.D.,¹⁸ Gur Jai Pal Singh, Ph.D.,¹⁹ Sandra Suarez Sharp, Ph.D.,³
 *Julie D. Suman, Ph.D.,²⁰ Marjolein Weda, Ph.D.,²¹ Janet Woodcock, M.D.,³ and Lawrence Yu, Ph.D.¹

Abstract

This March 2009 Workshop Summary Report was sponsored by Product Quality Research Institute (PQRI) based on a proposal by the Inhalation and Nasal Technology Focus Group (INTFG) of the American Association of Pharmaceutical Scientists (AAPS). Participants from the pharmaceutical industry, academia and regulatory bodies from the United States, Europe, India, and Brazil attended the workshop with the objective of presenting, reviewing, and discussing recommendations for demonstrating bioequivalence (BE) that may be considered in the development of orally inhaled drug products and regulatory guidances for new drug applications (NDAs), abbreviated NDAs (ANDAs), and postapproval changes. The workshop addressed areas related to *in vitro* approaches to demonstrating BE, biomarker strategies, imaging techniques, *in vivo* approaches to establishing local delivery equivalence and device design similarity. The workshop presented material that provided a baseline for the current understanding of orally inhaled drug products (OIPs) and identified gaps in knowledge and consensus that, if answered, might allow the design of a robust, streamlined method for the BE assessment of locally acting inhalation drugs. These included the following: (1) cascade impactor (CI) studies are not a good

*Corresponding author.

¹Food and Drug Administration, Center for Drug Evaluation and Research, Office of Pharmaceutical Science, Office of Generic Drugs, Rockville, Maryland.

²University of Iowa Hospitals and Clinics, Department of Pediatrics, Iowa City, Iowa.

³Food and Drug Administration, Center for Drug Evaluation and Research, Silver Spring, Maryland.

⁴Schering Plough Research Institute, Kenilworth, New Jersey.

⁵University of Maryland, Baltimore Maryland.

⁶GlaxoSmithKline, Research Triangle Park, North Carolina.

⁷University of Florida, Gainesville, Florida.

⁸School of Pharmacy, UNC at Chapel Hill, Chapel Hill, North Carolina.

⁹Department of Pharmaceutics, College of Pharmacy, University of Florida, Gainesville, Florida.

¹⁰Johns Hopkins University School of Medicine, Baltimore, Maryland.

¹¹Pfizer Global Research and Development, Sandwich, Kent, CT13 9NJ, United Kingdom.

¹²IPAC-RS, Washington, DC.

¹³Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut.

¹⁴Axar Pharma, Irvine, California.

¹⁵GlaxoSmithKline R&D, Ware, SG12 0DP, United Kingdom.

¹⁶Pfizer Limited, Ramsgate Road, Sandwich, Kent, CT13 9NJ, United Kingdom.

¹⁷Merck & Co Inc., West Point, Pennsylvania.

¹⁸Teva Pharmaceuticals, Horsham, Pennsylvania.

¹⁹Watson, Corona, California.

²⁰Next Breath, LLC, Baltimore, Maryland.

²¹National Institute for Public Health and the Environment (RIVM) Centre for Quality of Chemical-Pharmaceutical Products, Bilthoven, The Netherlands.

This summary may contain statements of opinion that do not necessarily reflect the opinions of the Food and Drug Administration, American Association of Pharmaceutical Scientists, Product Quality Research Institute or any other organization with which the authors are affiliated.

predictor of the pulmonary dose; more detailed studies on *in vitro/in vivo* correlations (e.g., suitability of CI studies for assessing differences in the regional deposition) are needed; (2) there is a lack of consensus on the appropriate statistical methods for assessing *in vitro* results; (3) fully validated and standardized imaging methods, while capable of providing information on pulmonary dose and regional deposition, might not be applicable to the BE of inhaled products mainly due to the problems of having access to radiolabeled innovator product; (4) if alternatives to current methods for establishing local delivery BE of OIPs cannot be established, biomarkers (pharmacodynamic or clinical endpoints) with a sufficiently steep dose–response need to be identified and validated for all relevant drug classes; and (5) the utility of pharmacokinetic studies for evaluating “local pulmonary delivery” equivalence deserves more attention. A summary of action items for seminars and working groups to address these topics in the future is also presented.

Table of Contents

Introduction	2
Background	3
Summary of Introductory Remarks	3
Summary of Podium Presentations	3
Current Challenges and Opportunities in Demonstrating Bioequivalence	3
The FDA Critical Path Initiative—Clinical Considerations	5
The FDA Critical Path Initiative— <i>In Vitro</i> Techniques and <i>In Vivo</i>	5
Imaging Technology	
Bioequivalence of Inhaled Corticosteroids	6
Device Design Similarity	7
International Regulatory Approaches to Bioequivalence	8
Challenges in Meeting International Requirements for Bioequivalence of Inhaled Drug Products	9
Statistical Approaches for Particle Size Distribution Data	10
Quality by Design for Orally Inhaled Drug Products	11
Summary of Breakout Sessions	13
<i>In Vitro</i> Approaches to Demonstrating Bioequivalence	13
Biomarker Strategies	15
Imaging Techniques	17
<i>In Vivo</i> Approaches to Establishing Local Delivery Equivalence	19
Device Design Similarity	22
Workshop Conclusions	24
Summary of Workshop Action Items	24
Acknowledgements	25
Author Disclosure Statement	25
List of Abbreviations	25

Introduction

THIS ARTICLE SUMMARIZES the proceedings and outcomes of the workshop on “Demonstrating Bioequivalence (BE) in Locally Acting Orally Inhaled Drug Products,” sponsored by the Product Quality Research Institute (PQRI) based on a proposal from the Inhalation and Nasal Technology Focus Group (INTFG) of the American Association of Pharmaceutical Scientists (AAPS). The mission of PQRI is to conduct research to generate specific scientific information that advances drug product quality and development. The INTFG’s objectives are to foster and advance the art and science of the pharmaceutical inhalation aerosol and nasal drug delivery systems, and to disseminate information relating to matters of scientific and technical interest related to these drug products, technology, and related processes.

This 2-day event was held on March 9–10, 2009, in Bethesda, MD, and provided a venue that brought together

participants and experts from Pharma and Generic companies, regulatory authorities, and academia from the United States, Europe, and the rest of the world. The objective of this workshop was to review, discuss, and consider, in a candid forum, potential recommendations for demonstrating BE that may be considered in the development of locally acting, orally inhaled drug products (OIPs) and regulatory guidances for new drug applications (NDAs), abbreviated NDAs (ANDAs), and postapproval changes.

The workshop began with a series of podium presentations, followed by moderated breakout sessions with focused discussions on the following selected topics:

- *In Vitro* Approaches to Demonstrating BE
- Biomarker Strategies
- Imaging Techniques
- *In Vivo* Approaches to Establishing Local Delivery Equivalence
- Device Design Similarity

Each breakout session was held three times to allow for maximum discussion and input from workshop participants. The moderators from each breakout session then presented a summary of the issues and discussion feedback to a general session. The podium presentations and synopses from the breakout sessions are available online at the PQRI Web site (www.pqri.org). This article presents a summary of speakers' presentations and the breakout session discussions. The breakout sessions provided background information and clarification on the specific topics, as well as consensus or disagreement on the usefulness of the suggested approaches for demonstrating BE.

Background

Several factors have converged to make a focused workshop on demonstrating BE in locally acting OIPs both timely and relevant. In March 2004, the FDA launched the Critical Path Initiative with the release of a report entitled "Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products"⁽¹⁾ to discern what challenges exist in moving a promising drug, biologic, or medical device along the critical path from discovery to a marketable product. On May 1, 2007, the FDA issued the Critical Path Opportunities for Generic Drugs⁽²⁾ report identifying many of the unanswered scientific questions that impede the development of generic versions of commonly used drugs. A key area identified in the FDA report as an opportunity for collaborative solutions is the need for establishing methods for assessing BE of inhalation products. In addition, the PQRI Aerodynamic Particle Size Distribution (APSD) Profile Comparisons Working Group completed a report evaluating the FDA-proposed statistical methods for comparing APSD profiles of Test (T) and Reference (R) products as part of the *in vitro* data supporting BE determination.⁽³⁻⁶⁾

Summary of Introductory Remarks

Janet Woodcock, M.D., U.S. Food and Drug Administration

BE problems have played out over time, especially for OIPs. OIPs will continue to be important in the future, and we need better BE methods. There are millions of people in the United States with respiratory disease. In the past, comparative clinical trials were used, but those are very difficult because they: (1) are not precise due to large variability between humans, (2) take a long time, (3) are confounded by several factors, and (4) are difficult to interpret.

For OIPs and transdermal products, traditional BE methods need improvement and new scientific approaches are necessary. This includes the:

- Need to identify new biomarkers,
- Need for better understanding of pulmonary pharmacodynamics (PD),
- Need for better understanding of the manufacturing science,
- Need for a detailed understanding of *in vitro/in vivo* correlations (IVIVCs) (e.g., particle size distribution to pulmonary deposition),
- Need for new clinical trial designs and better statistical approaches to ensure equivalence of safety and efficacy, and

- Need for new bioinformatic tools able to handle and manipulate the massive data acquisitions involved in drug development.

There are about four to five consortia under way, looking at biomarkers for regulatory science. None of these, however, involve OIPs. The consortia operate in a scientific pre-competitive space with shared scientific tools and techniques, without focusing on any proprietary products. Everyone can benefit from the shared understanding, and so these collaborations are pro-competitive. The Critical Path is trying to exploit the precompetitive space to work on standards so that drug companies and regulators can work on products. This exchange of information can lead to advancements in the field.

Methods for demonstrating BE for OIPs are important to make generics available in an orderly manner. Laying a path forward for novel BE methods is important.

Novel BE methods are also needed to help improve drug development, especially when delivery devices are involved. For example, how do we interpret results when small changes in the device are introduced?

Finally, novel BE methods and understanding are also needed to enable scale-ups. Performing a clinical trial for every scale-up is not efficient. However, the regulators need to know that a change is solid and well justified.

FDA needs standards and technologies developed to such a point that regulators can use them in reviews. But FDA is too stretched to do this alone, both for resources and expertise. FDA, therefore, welcomed experts from academia, industry, and consortia to participate in this workshop. This workshop was similar to the Critical Path initiatives and consortia on biomarkers and clinical trials.

Summary of Podium Presentations

Current Challenges and Opportunities

in Demonstrating Bioequivalence

Gur Jai Pal Singh, Ph.D., Watson Pharmaceuticals

Acceptable BE studies are essential for approval, and serve as a basis for safety and effectiveness of generic drugs. BE studies may also be employed at certain stages of the development and approval process of new drugs. The objective of this talk was to provide an overview of the current challenges in establishing BE for OIPs. Beginning with a review of the fundamentals of establishing BE of multisource products, the presentation included an understanding of the FDA paradigms for demonstrating BE of OIP, discussed the complexities in the conduct and evaluation of *in vitro*, pharmacokinetic (PK) and PD studies, and highlighted the challenges of the approaches used for conventional solid oral dosage forms when applied to OIP.

Methods for determination of BE may vary with the drug product and its route of administration. The regulation 21 CFR 320.24(b) provides a list of approaches for documentation of BE, including (1) *in vivo* studies in humans comparing drug/metabolite concentrations in an accessible biological fluid, (2) *in vivo* testing in humans of an acute pharmacological effect, (3) controlled clinical trials in humans to establish safety and efficacy, (4) *in vitro* methods, and (5) any other approach deemed adequate by FDA. One or more of these approaches might be necessary for demonstration of

BE of the T and R products. For example, in the generic drug applications approved by the FDA, BE of solid oral dosage forms intended for systemic delivery is based on *in vivo* PK studies supported by comparative *in vitro* dissolution data. This approach has been successfully applied to a large number of drug products for which the systemic circulation provided the sole route of drug delivery to the target site(s), regardless of the modes of action of the active moieties and indications for clinical use.

However, the above approach has been considered insufficient for documentation of BE of OIP due to the potentially limited relevance of PK data to drug delivery to the local site(s). For OIPs, drug that is present in the systemic circulation is due to absorption from the local site of action (lung) and to absorption from other sites [oropharyngeal cavity and gastrointestinal (GI) tract] that are anatomically and physically distinct from the target local site (lung). Based on the available information, the FDA determines OIP BE using a "weight-of-evidence" approach that includes evidence for qualitative and quantitative sameness of formulations, equivalence with regard to *in vitro* performance in drug delivery, systemic exposure, and drug delivery to the local site(s) of action.

Establishment of BE of OIP based on this FDA paradigm offers challenges with establishment of all four elements of the "weight of evidence." For the generic drug manufacturers, determination of quantitative sameness of formulations can be challenging. Determination of *in vitro* drug delivery involves several tests. Furthermore, comparative *in vitro* testing is necessary at multiple sectors of the product use, because the OIP are generally multiple dose products. Therefore, the evidence for equivalent *in vitro* performance based on certain *in vitro* tests warrants testing at multiple sectors. This represents a considerable challenge compared with *in vitro* dissolution testing at one or more pH values that may be sufficient to demonstrate comparative *in vitro* performance of most solid oral products.

Methods for determination of systemic exposure equivalence based on PK measurements for OIP and oral products may be similar with respect to study design, determination of drug in biological fluids, statistical analysis, and acceptance limits for regulatory approval. However, the conduct of *in vivo* BE studies of OIP offer challenges in maintaining interoccasion reproducibility in dose delivery due to variable inspiratory flow rates and difficulty in coordination of drug actuation and inhalation. The extent of interoccasion variability in dose delivery can enormously contribute to the observed intrasubject variability influencing both the sample size and study design for demonstration of equivalence of systemic exposure (as well as local delivery) from the T and R products.

Among the four components of the "weight of evidence," establishment of equivalence in local delivery of OIP is by far the most challenging, principally due to the lack of a single marker (like blood concentrations for oral products) that can be used to objectively quantify drug delivery to the local site. The OIP represent a number of drug products with distinct modes of action. Therefore, the choice of biomarker, target population, and study design may vary with the drug product. In the past, the FDA has accepted both bronchodilatation and bronchoprovocation study de-

signs for documentation of BE of albuterol metered dose inhalers. However, the BE study designs used for this short-acting beta-agonist (SABA) may or may not be applicable to determination of BE of long-acting beta-agonists (LABAs), and may have no utility for establishment of BE of inhaled drugs with no measurable acute effect (e.g., corticosteroids).

The challenge in demonstrating equivalence in local delivery appears formidable when evaluating OIP formulations containing combination drugs (e.g., a beta-agonist and a corticosteroid). The presentation included published information from the Physician's Desk Reference labeling of the Advair® DPI (dry powder inhaler), which contains salmeterol xinafoate and fluticasone propionate. The clinical study design included comparison of the bronchodilatation activity of the combination product to those of the inhalers containing the individual drugs salmeterol xinafoate and fluticasone propionate. A direct application of this approach for evaluation of equivalence in local delivery from generic combination inhalers may be complicated due to a number of factors. However, to be consistent with the Office of Generic Drugs' (OGD) general recommendations for combination drug products, it will be important that the BE studies separate contributions of the two individual drugs to systemic exposure and local delivery following administration of the generic and R combination products.

Clinical measurements of local effects of single and multiple doses of OIP generally lack dose proportionality. The steepness of the dose-response relationship which, along with variability, determines the ability of a bioassay to distinguish between the single- and multiple-actuation doses of a drug product may be influenced by a number of factors including the drug, biomarker, disease severity, and precision and sensitivity of measurements. The observed lack of linearity in dose-response adds another complexity in documentation of BE of these drug products. In the presence of nonlinear dose-response relationships, the observed difference in response may not be a simple function of the difference in the dose delivered to the target site. The magnitude of difference in the response may also vary with the positioning of the observed responses on the nonlinear dose-response curve. The selection of adequate sample size may be influenced by both the slope of and variability in the dose-response.

In the case of an orally administered drug product, OGD generally grants waiver of *in vivo* BE testing for lower strengths based on (1) acceptable *in vivo* BE study(ies) on the high strength product, (2) formulation proportionality between the strengths, and (3) comparative *in vitro* dissolution of all strengths of the T products. However, application of this approach for consideration of waiver of *in vivo* testing for the lower strengths of OIP is complicated, in part due to the lack of linearity in the PD response over the clinically relevant dose range.

In conclusion, conventional approaches used for determination of BE of oral drug products may not be directly applicable to establishment of BE of OIP. The factors that add to complexity in application of the conventional approach to determination of BE may also influence scientific considerations applicable to waivers of *in vivo* testing for the lower strengths and establishment of IVIVCs.

*The FDA Critical Path Initiative—Clinical Considerations
Badrul Chowdhury, M.D., Ph.D., U.S. Food
and Drug Administration*

For an OIP to be approved as a generic equivalent to a R product through the ANDA process [section 505(J) of FD&C Act], BE must be demonstrated in addition to meeting other criteria. There is prior precedence and generally accepted models for demonstrating BE, such as use of methacholine challenge for bronchodilators, for example, albuterol.⁽⁷⁾ In contrast, for inhaled corticosteroids (ICS) demonstration of dose–response is difficult with currently established clinical methods because the dose–response is flat.⁽⁸⁾ If, for example, a two-fold difference in dose cannot be detected for a reference ICS, then a generic product could deliver half as much or twice as much as the R product without detection of the difference. Therefore, FDA’s Critical Path Initiative provides an opportunity to develop new methods and approaches, such as novel PD study design or use of biomarkers to determine BE.

Measurement of exhaled nitric oxide (eNO) offers promise as a biomarker to detect differences in dose of ICS delivered to the relevant sites of action in the airways. It is a biologically relevant marker that is increased in persistent asthma.⁽⁹⁾ and decreased in a dose-dependent manner by administration of ICS at clinically relevant doses.⁽¹⁰⁾ Also, eNO is not affected by bronchodilators⁽¹¹⁾ so this method could be used to measure dose–response of the ICS component of a combination product containing a LABA. The use of eNO is suitable for crossover BE studies because both the onset and offset of ICS effect are reasonably rapid⁽¹²⁾ and reproducible.⁽¹³⁾ Also, the methodology for measuring eNO is standardized and harmonized.⁽¹⁴⁾

There are several limitations to the use of eNO. First, eNO is elevated in atopic individuals without asthma and in several other diseases such as chronic obstructive pulmonary disease (COPD) during an exacerbation, bronchiectasis, and viral respiratory infections. Second, the dose–response with ICS may be dependent on the baseline eNO concentration. Subjects with levels >100 ppb show the steepest dose–response, whereas those with lower levels may have a flat–dose response to ICS.⁽¹⁰⁾ Third, subjects currently being treated with an ICS may not be suitable for a BE study unless the ICS can be safely withdrawn prior to the study. Therefore, careful subject selection plays an important role in the likelihood of this approach succeeding.

As part of FDA’s Critical Path Initiative, the agency has funded an exploratory study at National Jewish Health in Denver, CO.⁽¹⁵⁾ The objectives of the study are to evaluate eNO as a marker for demonstrating ICS dose–response by evaluating the time course of various doses of fluticasone propionate (FP) on eNO. Subject inclusion criteria are ages 18 to 65 years, mild to moderate persistent asthma, bronchodilator reversibility of airway obstruction and eNO ≥ 45 ppb. Subjects will begin a 14-day placebo run-in during which previous ICS therapy will be withdrawn. Those with an eNO ≥ 45 ppb will then enter a 14-day period of treatment with FP 88 μg twice a day (b.i.d.). Those subjects with a $\geq 25\%$ decrease in eNO and reproducible measurements at the end of this first phase will then enter a 14-day placebo washout. Those subjects whose eNO returns to within 10% of baseline will enter phase 2 of the study. This phase will be a four-way,

12-sequence crossover of 44, 88, and 352 μg b.i.d. each for 14 days and separated by a 14-day washout. Throughout the study, eNO will be measured every other day. Also, spirometry and methacholine challenge will be performed at intervals. From the results of this study, FDA will be able to determine the suitability of eNO as a biomarker for determining dose–response to an ICS.

FDA has funded a second study⁽¹⁶⁾ at the University of Iowa to evaluate the suitability of the asthma stability model⁽¹⁷⁾ for determining dose–response to ICS. In this model, subjects are treated with either a short course of oral corticosteroid or high-dose inhaled steroid to maximize lung function (wash-in). The subject is then treated in a randomized crossover manner with 4 weeks of one dose of FP and asthma stability is measured by forced expiratory volume in one second (FEV₁) and eNO. At the conclusion of the 4-week treatment, the corticosteroid wash-in is repeated and the next dose of FP is initiated. By using a wash-in, the problem of carryover between treatments is circumvented and the ability of a given dose to maintain asthma stability is measured. The % decrease in FEV₁ is then plotted against dose to obtain a dose–response curve. A previous pilot study of this method suggested that ICS dose–response can be demonstrated for FEV₁. The results of this study will indicate whether eNO provides greater power than decline in FEV₁ and how the high dose ICS wash-in compares to a wash-in with oral corticosteroids.

*The FDA Critical Path Initiative—In Vitro Techniques
and In Vivo Imaging Technology
Anthony J. Hickey, Ph.D., University of North Carolina*

The cycle of development of a product begins with the discovery of the drug, its preparation, its *in vitro* and *in vivo* performance and, ultimately, its therapeutic effect in clinical trials.⁽¹⁸⁾ A predictive link between the *in vitro* and *in vivo* performance would be highly desirable, and is central to the concept of BE. For aerosol products, the sequential steps in performance characterization, representing one part of the development cycle, for which a correlation might be sought, are *in vitro* measures of delivered dose and APSD and the *in vivo* measure of lung deposition. These *in vitro* characteristics are important quality measures, whereas lung deposition is an element that contributes to the final efficacy of the product.

Inertial impaction is the method described in regulatory guidance documents and pharmacopeias to characterize the APSD. Historically, this method was employed for sampling ambient aerosols and was adopted by pharmaceutical scientists because of: (1) the relevance of aerodynamic diameter to lung deposition, (2) expression of particle size distribution (PSD) in terms of mass (dose), (3) ability to sample the entire dose, and (4) chemical detection of drug. However, it is important to remember that an impactor is not analogous to the lungs. The lungs are, as a whole, an excellent filter, but each airway generation does not exhibit a step function collection efficiency as do stages of the impactor. This may be explained in terms of features of the impactor including: operating at a fixed flow rate; having increasing linear velocity as penetration to lower stages occurs (due to reduced jet sizes); and its rigid, robust and well-defined construction. None of these features are characteristics of the lungs or

regions within them. These differences pose difficulties in extrapolating stage deposition in an impactor to lung deposition despite the knowledge that the aerodynamic sizes measured by an impactor can be related to lung deposition as evidenced by the large body of literature in the industrial hygiene, occupation, and environmental medicine literature.^(19,20) It is known, for example, that differences in inspiratory flow of patients often result in changes in particle size distribution of aerosols delivered by passive DPIs.⁽²¹⁾ This, in turn, might be expected to influence lung deposition, but a quantitative relationship has been elusive. Clearly, studying lung deposition would assist in developing a relationship between *in vitro* performance and therapeutic effect.

Three techniques have been employed for imaging aerosols deposited in the lungs: planar gamma scintigraphy, single photon emission computed tomography (SPECT), and positron emission tomography (PET). The former examples use passively radiolabeled, frequently with technetium in some form, aerosol particles or droplets, that can be imaged by single or multiple head gamma cameras. Invoking multiple heads increases cost and reduces the number of sites at which studies can be conducted. PET labels the drug itself, which requires neutron activation and a cyclotron, all of which are expensive, time consuming, and inconvenient. Nevertheless, spatial resolution is increased as 2D images (gamma scintigraphy) are developed to 3D images (SPECT) and sensitivity is increased (PET). Currently, gamma scintigraphy is the most frequently used technique. Two important questions require an answer before gamma scintigraphy can be proposed as a routine method for regulatory purposes: (1) is there sufficient protocol agreement from one laboratory to another about data presentation [central to peripheral (C/P) ratio; region of interest definition, etc.] to allow comparison; and (2) will regulators ever accept that passive labeling, which changes the formulation composition, does not represent adulteration which implies the T sample is unrepresentative of the product? These questions were taken up in the breakout discussions.

Some hope for an IVIVC was recently given by Newman and Chan⁽²²⁾ who found that for a variety of commercially available inhalers there appeared to be a linear relationship between lung deposition, measured by gamma scintigraphy, and mass of particles $<3\ \mu\text{m}$ in aerodynamic diameter. The authors were clear that this data should be interpreted with caution. It should also be remembered that this does not speak to regional deposition in the lungs which, it might be supposed, relates to receptor targeting and ultimately to therapeutic effect. Enquiry into regional targeting may be an opportunity to validate lung deposition modeling with experimental data. In this regard, recent developments have shown that an onion peel approach to interpretation of SPECT data can be correlated well with regional deposition in the lung, despite the inevitable probabilistic interpretation of lung deposition data with respect to proportion of any particular airway generation represented in a concentric view of the lungs as a single organ system.⁽²³⁾ Factors that complicate interpretation of the importance of lung deposition to efficacy include the absence of specific knowledge about target receptor location.

It may be concluded that estimation of APSD and delivered dose are important quality measures that are known to impact efficacy. Inertial samplers are not analogous to lungs, in that stage deposition cannot be dissected to indicate regional lung deposition, but they may be used to indicate broadly the probability of lung deposition, perhaps in terms of a single particle size cutoff or a narrow range depending on clinical population. Greater relevance of size fractions in the distribution to regional deposition may be extracted from lung deposition models, in which particle size characteristics of the aerosol play an important role. Progress has been made in validating a particular lung deposition model. Development of standard protocols for experimental design and data interpretation, with respect to lung imaging in conjunction with validated mathematical models, may increase the potential of lung deposition studies to influence decisions regarding equivalence of products. However, a serious barrier to regulatory adoption of imaging techniques is the passive labeling technique, which is currently viewed as adulteration.

Bioequivalence of Inhaled Corticosteroids
Günther Hochhaus, Ph.D., University of Florida

For the BE testing of inhalation drugs, the FDA currently limits PK studies to the assessment of the systemic exposure. PK studies are not accepted as a tool to assess the pulmonary activity of inhalation drugs, as it has been stressed that the sampling site for PK (plasma) is a compartment that is downstream of the lung. Thus, clinical endpoints have been suggested for testing pulmonary equivalence. However, the flat dose-response profiles of ICS represent a challenge and traditional clinical approaches as well as studies with improved study design (eNO; Ahrens' asthma stability model) have not yet proven to show sufficient sensitivity necessary for BE studies. This presentation hypothesized that PK tools might be a valuable alternative to clinical studies for assessing the pulmonary fate if they can provide "high-resolution" information on three key questions determining the local BE of inhalation drugs. Key question 1 relates to the extent of pulmonary deposition. Key question 2 relates to the regional deposition within the lung, that is, C/P ratio. Key question 3 relates to the systemic absorption rate. It was hypothesized that if PK studies can provide answers to these questions, BE studies based on PK approaches should be possible.

As detailed PK studies showing the full potential of PK for evaluating pulmonary equivalence are not yet available, this presentation reviewed results of trial simulations that incorporated in detail the pulmonary fate of inhaled glucocorticoids and its adherent variability into the model. This "physiological" modeling approach allowed investigation of whether local PK characteristics determining pulmonary efficacy (drug dissolution rate, central vs. peripheral deposition, the effects of mucociliary clearance, and other factors) will also affect plasma concentration profiles. The results of these clinical trial simulations suggested that area under the concentration-time curves (AUC) and C_{max} in healthy volunteers (HVs) and asthmatics are likely to shed light on the pulmonary fate of ICS. These simulations performed for fluticasone propionate (FP) as a model glucocorticoid suggested that the area under the concentration-time profiles is highly suitable to detect differences in the pulmonary

deposited dose if studies are performed for ICSs with negligible oral BA (Key question 1). Assessment of the pulmonary available dose can be extended to ICS showing distinct oral absorption if studies are performed under charcoal "block" that prevents oral absorption.

For lipophilic ICS with slow dissolution rates (such as FP, beclomethasone dipropionate, mometasone furoate), AUC estimates in HVs are sensitive to the geography of deposition (central vs. peripheral deposition), as a more central deposition will result in a more distinct removal of slowly dissolving drug particles through the mucociliary transporter that is more active in the central portions of the lung. Simulations predicted that rather small differences in the C/P ratio will result in significant differences in the AUC estimates. Thus, AUC estimates will also be able to detect differences in the C/P ratio between generic and innovator (key question 2). To exclude that special, while unlikely, scenario where differences in both dose and C/P ratio (the generic delivers a lower respirable dose more peripherally, or a higher respirable dose more centrally) will result in similar AUC estimates while BE is not warranted, studies in asthmatics might have to be performed. This is because the shift of the C/P ratio in asthmatics to more central deposition, would allow the detection of differences in the respirable dose. Alternatively, *in vitro* tests might assess differences in the respirable dose.

The presented simulations also suggested that differences in the absorption rate of generic and innovator (key question 3) are best mirrored by monitoring C_{max}, while parameters such as the mean residence and mean absorption time are less sensitive.

Based on the presented simulations, the following studies should be suitable to assess BE (Fig. 1). However, well designed PK studies need to be performed in the future to validate this approach.

Device Design Similarity
David Parkins, Ph.D., GlaxoSmithKline

When considering the impact of device differences on the BE of an inhaled product, it is important to recognize that the safety and efficacy of that product when used by the patient is reliant not only on the device, but also the formulation and the way the patient uses the device. Assessing the impact of device differences on product BE is therefore not straightforward. The lack of discriminating *in vitro* methodologies to assess differences in device design further complicates any such assessment.

Inhalation products can be broadly classified into DPIs and pressurized metered dose inhalers (pMDIs); both types are complex drug products with the dose delivered being dependent on the device design and its operation.

pMDIs deliver the dose to the patient in a ballistic manner, with their performance being dependent on the integration of the formulation, valve, can, and actuator. For pMDIs, the aerosolization process is dictated by the formulation/device combination selected with differences potentially leading not only to changes in APSD, but also to aerosolization timing, plume geometry, and mouth feel. As pMDIs can be used in combination with ancillary devices such as counters and spacers, consideration needs to be given to the impact of device design on the performance of the pMDI/ancillary device combination.

In contrast to pMDIs, DPIs have a greater diversity of designs and operating principles, with the majority of designs relying on the patients inhalation maneuver (inspiratory force along with appropriate technique) to aerosolize the formulation. Therefore, in addition to formulation and device design differences, consideration needs to be given to the impact of device design on airflow resistance and flow rate dependency.

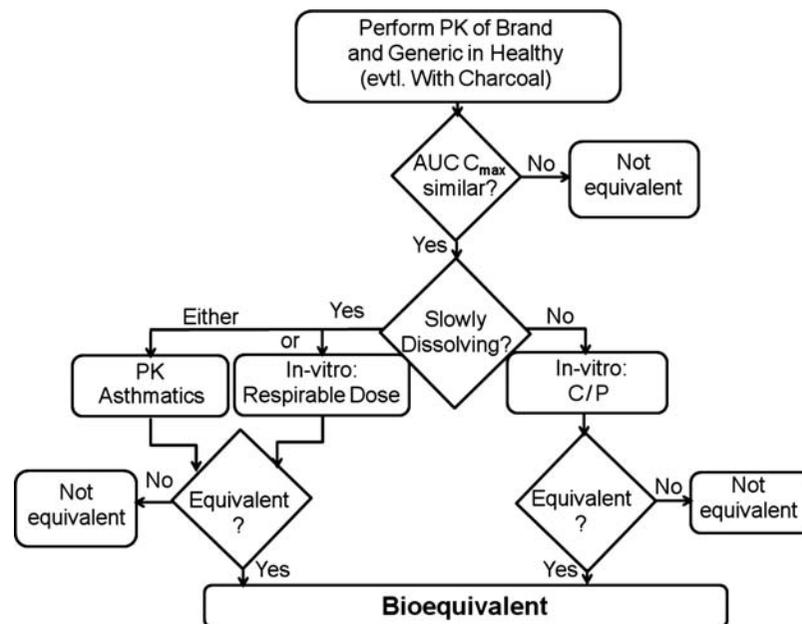


FIG. 1. Proposed flow chart for PK-based BE testing.

A recently published case study⁽²⁴⁾ described studies performed to assess the *in vitro* performance, pharmacokinetics, and safety and efficacy of two Salmeterol 50 µg/ Fluticasone Propionate 250 µg DPIs. The two DPI devices studied were a reservoir powder inhalation device (RPID) and a Diskus® multiple-dose inhaler. These two devices had a large number of similarities including the formulation used and airflow resistance. However, they did differ in terms of their device shape and metering principles. *In vitro* CI testing showed the two devices to have comparable emitted doses and fine particle mass (0.8–6.2 µm by Andersen Cascade Impactor). A 12-week double-blind double dummy study in 270 moderate asthmatics concluded the two devices were clinically equivalent in terms of morning peak flow (PEF), and were well tolerated with comparable safety profiles. However, an *in vivo* PK/PD study showed the systemic exposure to be double for one device (RPID) versus the Diskus®.

The *in vitro* APSD profiles for the two devices were considered to be comparable. The small differences noted did not appear sufficient to explain the observed twofold increase in systemic exposure. Potential reasons for the lack of correlation between the systemic exposure and the *in vitro* data were then discussed; these were broadly categorized as being either due to inadequacy of the *in vitro* test or due to differences in the way the patient interacted with the device.

Although cascade impaction methods are widely used as quality control (QC) tests they do have limitations when being used to predict BA. For example, they are typically operated at fixed flow rates and rely on deposition by impaction rather than impaction, sedimentation, and diffusion as would occur *in vivo*. Similarly, it has been established that the induction port of an impactor poorly predicts actual oropharyngeal deposition *in vivo*.

Consideration was given as to whether the difference in device design influenced the way the patient interacted with the device in a way that would not be detected by the *in vitro* test. For example, mouthpiece design influences how wide the mouth is opened during inhalation and mouthpiece diameter can impact deposition efficiency.⁽²⁵⁾ Similarly, it is well known that correct operation and inhalation technique is the key to therapeutic outcome. Differences in design mean that critical steps can vary from device to device,⁽²⁶⁾ rates of patient/device critical errors vary between devices,^(27,28) and mishandling can lead to patients inhaling unnecessarily slowly.⁽²⁹⁾

The conclusion of the RPID/Diskus study was that despite many similarities between the two devices the clinical efficacy/tolerability profile was clearly influenced by other factors. These factors related to formulation, device, *in vitro* test, and/or patient handling. The lack of correlation between *in vitro* performance and *in vivo* performance suggested that, in this case, reliance on *in vitro* data alone would not have detected the twofold difference in systemic PK/PD effects for one of the inhalers.

International Regulatory Approaches to Bioequivalence
Marjolein Weda, Ph.D., National Institute for Public Health
and the Environment, The Netherlands

In January 2009, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) adopted the "Guideline on the Requirements for

Clinical Documentation for Orally Inhaled Products (OIPs), 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 (CPMP/EWP/4151/00 Rev.1)."⁽³⁰⁾ This guideline is a revision of the "Points to Consider on the Requirements for Clinical Documentation for Orally Inhaled Products (CPMP/EWP/4151/00),"⁽³¹⁾ and was issued to clarify the types of studies to be performed when demonstrating therapeutic equivalence between two OIPs. The guidance is intended for abridged applications as well as for variations and extensions to existing marketing authorizations in the European Union (EU).

Currently, there are several methods available for equivalence testing of OIPs, including: (1) *in vitro* comparison; (2) pulmonary deposition studies using imaging techniques or PK measurements; (3) PD studies; and (4) phase 3 clinical trials. In general, the method with the highest chance of detecting a clinically relevant difference between two OIPs should be the method of choice. Based on this principle, the CHMP guideline incorporated a stepwise approach to establish the most suitable method or combination of methods. A simplified depiction of this approach is shown in Figure 2. The extensive prerequisites for the application of certain methods as well as various considerations that need to be taken into account when designing the equivalence study are elaborated in the guideline.

In some cases, comparative *in vitro* data may be considered acceptable if the T product satisfies all of the following criteria:

- The product contains the same active substance (i.e., the same salt, ester, hydrate, or solvate).
- The pharmaceutical dosage form is identical (e.g., pMDI vs. pMDI).
- If the active substance is in the solid state (powder, suspension): any differences in crystalline structure and/or polymorphic form should not influence the dissolution characteristics, the performance of the product, or the aerosol particle behavior.
- Any qualitative and/or quantitative differences in excipients should not influence the performance of the product (e.g., delivered dose uniformity), aerosol particle behavior (e.g., hygroscopic effect, plume dynamic, and geometry), and/or be likely to affect the inhalation behavior of the patient (e.g., PSD affecting mouth/throat feel or "cold Freon" effect).
- Any qualitative and/or quantitative differences in excipients should not change the safety profile of the product.
- The inhaled volume through the device to enable a sufficient amount of active substance into the lungs should be similar (within ± 15%).
- The handling of the inhalation devices for the T and the R products to release the required amount of the active substance should be similar (within ± 15%).
- The inhalation device has the same resistance to airflow (within ± 15%).
- The target delivered dose should be similar (within ± 15%).

In practice, this implies that the demonstration of therapeutic equivalence by comparative *in vitro* testing with CI analysis

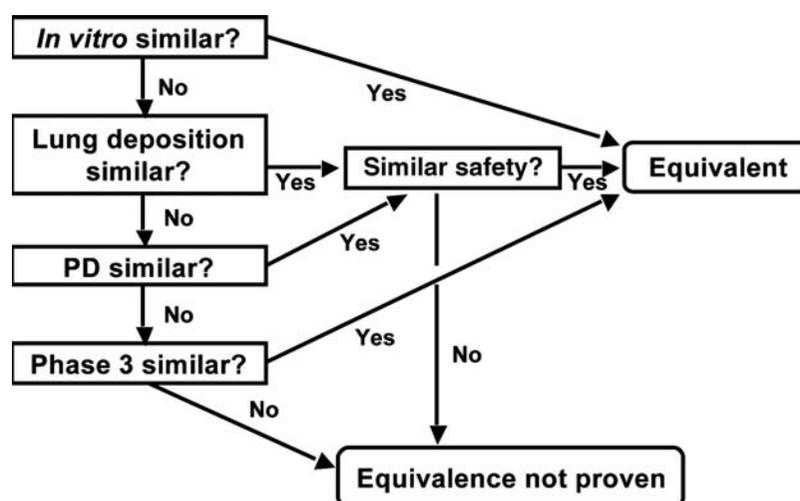


FIG. 2. Stepwise approach in EMEA guideline.

alone is normally not sufficient. Frequently, such a study should be supported by and supplemented with other types of *in vitro* tests, such as comparison of solid particle crystalline structure and inhalation device resistance to airflow in the case of dry powders for inhalation.

Despite the concise criteria that would allow the *in vitro* comparisons to serve as proof of equivalence, there are still several challenges that need to be addressed before comparative *in vitro* testing will be broadly accepted by regulatory authorities for a wide range of products. These challenges concern the test methods as well as the acceptance criteria. For example, to show compliance with the above-mentioned prerequisites, standard test methods should be developed for investigating the influence of a difference in crystalline structure and/or polymorphic form on dissolution and on crystal growth of the aerosolized particles. Moreover, for a considerable number of prerequisites, acceptance criteria should be established. These acceptance criteria must guarantee that any differences that will inevitably be seen between a T and R product will not lead to clinically relevant differences. It is, for example, not exactly known what differences in hygroscopic effect, plume dynamics and geometry, and dissolution behavior can be accepted. Most likely, the acceptance criteria may differ between the various (classes of) active substances.

The CI analysis needs special attention with respect to the choices of the stage grouping, the range of flow rates to be tested, and the maximum allowable *in vitro* differences that are not expected to influence efficacy and safety. Moreover, the statistical methods to be applied are still under debate, and will determine the number of batches/lots to be tested.

Moreover, companies are encouraged to adopt a (more) scientific approach for the justification of the choices made with respect to the methods as well as the acceptance criteria applied. There is a lot of information available in the public domain that could serve as supportive argumentation, for example, information on steepness of dose-effect curves, PK, therapeutic index, lung deposition, *in silico* predictions, and studies that combined *in vitro* studies with *in vivo* studies. Companies and academia, however, are encouraged to enlarge the knowledge in the field of *in vitro* equivalence testing to fill the knowledge gaps and possibly relax the current, rather strict *in vitro* requirements of the EMEA guideline.

Irrespective of the kind of comparative *in vitro* studies that will be performed, the choices for the study designs and the acceptance criteria must be made before the start of the investigations, and should be included in a preestablished protocol in the same way a clinical trial protocol would be developed.

Challenges in Meeting International Requirements for Clinical Bioequivalence of Inhaled Drug Products
Tushar Shah, M.D., Mark Lepore, M.D.,
and Paul Dorinsky, M.D., Teva Pharmaceuticals

Several regulatory guidelines are available outside of the United States for demonstrating BE of OIPs.^(30,32,33) In addition, members of the FDA have shared their expectations for the development of generic OIPs at various association conferences.⁽³⁴⁾

Each regulatory agency has outlined a different approach for the development of OIPs; however, one common element required by most agencies for demonstrating clinical BE is the need to show a dose-response relationship between the T and R OIPs. Although the need to demonstrate a dose-response in a clinical trial to determine BE is scientifically justifiable, because it establishes assay sensitivity and supports study validity, the existence of a flat dose-response relationship for bronchodilators and ICS makes this requirement nearly impossible to achieve. This is especially challenging if the traditional BE limits of 80–125% are used. The availability of many OIPs at only a single strength, which is on the flat part of its dose-response relationship, adds another level of complexity in fulfilling this objective.

There are a number of statistical methods to analyze dose-response relationships. One commonly used method is the Finney Bioassay,⁽³⁵⁾ which establishes the relative potency ratio for two treatments using two or more doses of both the T and R products. However, for OIPs such as bronchodilators and ICS where the dose-response relationship is shallow, this method will result in wider confidence intervals relative to OIPs where the dose-response relationship is steeper. For these common OIPs, statistical simulations demonstrate that the sample size required to achieve reasonable study power (e.g., 80–90%) would easily reach several

hundred patients per treatment arm, assuming that the BE limits of 0.8–1.25 are utilized.

An ideal clinical efficacy study design for establishing a dose–response needs to (1) be sensitive (i.e., utilize OIPs with steep dose–response slopes); (2) be reproducible; (3) have low inter- and intrasubject variability; and (4) be achievable with manageable patient numbers (i.e., with respect to the confidence interval required for establishing BE).

For bronchodilators, two study designs have been used with some success to demonstrate dose–response relationships: bronchodilation and bronchoprotection. For formoterol, limited data is available with the bronchoprotection study design for demonstrating a dose–response relationship. In the 1990s, Becker and Simons,⁽³⁶⁾ as well as Lipworth et al.,⁽³⁷⁾ were able to detect a dose–response following single doses of formoterol. However, the latter study was not able to detect a dose–response when formoterol was administered chronically, which was likely due to the development of tachyphylaxis that occurs with these drugs during chronic use. For demonstration of relative potency for albuterol-containing products, a bronchoprotection study design was able to detect a dose–response and establish BE with low numbers of subjects ($n = 18–24$) and correspondingly wide confidence intervals.^(38–40)

Several studies have successfully used a bronchodilation study design for demonstrating a dose–response to formoterol, especially when a wide range of formoterol doses was used. When the dose range of formoterol was only twofold, the ability to detect a dose–response was limited or not possible.^(41–45)

Both of these study designs have been used successfully to discriminate doses for bronchodilator drugs as long as the confidence interval was wider than the standard limit used for establishing BE (0.8–1.25), and the doses evaluated were more than twofold apart.

For ICS, there does not appear to be a study design or efficacy measure that has consistently been able to discriminate doses. Even though novel designs have been explored, their reproducibility and reliability have yet to be demonstrated. For example, there have been three successful studies using exacerbations,⁽⁴⁶⁾ FEV₁,⁽⁴⁷⁾ and an asthma stability⁽¹⁷⁾ model for demonstrating a dose–response relationship to ICS. However, other studies, in some cases using similar designs, were not able to detect a dose–response. Similarly, although several studies have suggested that eNO may be able to discriminate doses of ICS,^(10,48–51) significant limitations in study design raise questions on the utility of this model for detecting dose–responses to ICS. For instance, because a number of these studies utilized a cumulative-dose design, the observed dose–response relationship may have been due to a period effect rather than a dose effect. The current evidence suggests that additional studies are needed with these various study designs to confirm their usefulness for showing a dose–response to ICS before they can be acceptable as standards used for regulatory submissions. Among the study designs that have been examined to date, eNO and asthma stability clinical study designs seem to hold the most promise; but even for these study designs, more than doubling of the dose and a wider confidence interval will be needed to demonstrate BE.

In addition to the challenges associated with showing a dose–response to ICS and bronchodilator drugs, practical

limitations also exist that add further complexity to establishing BE for OIPs. There is a lack of clarity on how to handle OIPs with multiple strengths. Having to demonstrate a dose–response at each strength would be essentially impossible for the higher strength products. How to handle OIPs containing two active drug substances (e.g., ICS/LABA combination products) needs to be defined, where the ability to distinguish doses will be even more difficult. Lack of availability of placebo devices for the R products also could prevent the conduct of blinded studies.

If clinical study models that can consistently and reproducibly demonstrate dose–response relationships for the common OIPs cannot be identified, then alternative approaches to demonstrating BE need to be considered. These include consideration of: (1) the use of *in vitro* data for determining BE; (2) the EU approach of using PK with and without charcoal to establish the total and lung specific drug absorption profiles; (3) the Canadian approach for ICS using sputum eosinophils as a marker with a single dose of the T and R products compared with placebo; and (4) an approach accepted for nasal suspension sprays where a single dose of the T and R products are compared with placebo treatment in a clinical trial using traditional measures of efficacy and safety. Hopefully, further discussions (e.g., at the upcoming PQRI workshop on the use of PK for demonstrating *in vivo* BE for OIPs) could bring us closer to identifying a scientifically valid solution that can fulfill regulatory needs and that can be more readily and reproducibly accomplished.

Statistical Approaches for Particle Size Distribution Data David Christopher, M.S., Schering-Plough

This presentation began with a brief overview of CI and APSD profiles and a comparison of three statistical approaches: Chi-square, f2 Similarity Factor, and Multivariate Bioequivalence (MVBE).

There was a discussion of how a statistical test may correctly meet some objectives (e.g., unbiasedness, scaled to R product variability, etc.) but fail to have enough power to detect differences of practical importance. Also discussed was the difficulty in establishing a “target” (i.e., consensus on profiles that are, or are not, equivalent) against which the performance of a statistical test can be judged.

A brief summary of the work of the PQRI Profile Comparisons Working Group was given, explaining the FDA-proposed chi-square ratio test and the use of simulations to generate realistic APSD profiles based on real data to evaluate the performance of the test. An example of CI profiles used in the chi-square test evaluation is given in Figure 3.

Chi-square ratio test

- FDA proposal requires 30 CI runs for T and 30 CI runs for R
- Calculates chi-square ratio as an overall measure of “distance” between T and R APSD profiles, scaled to the R product variability
- Uses resampling to create a distribution of these ratios
- Uses the 95th percentile of this distribution as the test statistic
- A smaller chi-square ratio means more similar profiles.

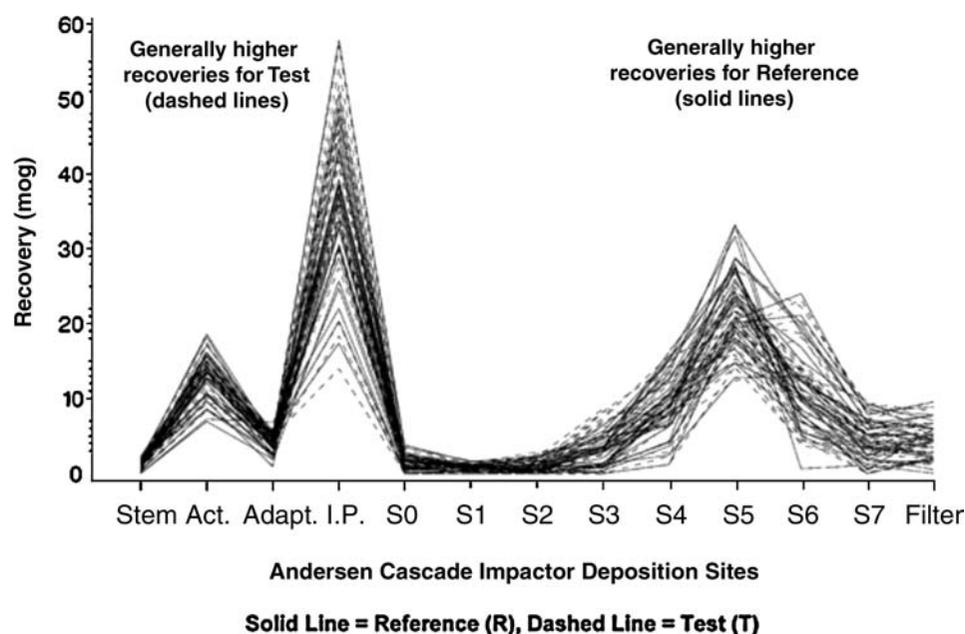


FIG. 3. Spaghetti plots of C.I. data from 30 runs with the R Product and 30 runs with the T Product. The lines connecting the data points at the deposition sites are provided as a visual aid and have no physical meaning.

f2 or similarity factor test

- Developed for comparing dissolution profiles, but could potentially be applied to APSD profiles
- A population measure for assessing the similarity of two profiles
- Based on squared differences of cumulative distribution of T and R
- Requires ordering of deposition sites
 - straightforward for inside impactor sites
 - how to treat outside impactor sites?
- No R product variability scaling
- In dissolution testing, similarity factor of 50 or greater indicates “similar” profiles

Multivariate PBE (MVBE)

- Generalizes univariate PBE, including R product variability scaling
- Originally developed with *in vitro* BE in mind; for example, treating four measures of spray pattern together in a single test rather than as four separate tests
- Shown statistically valid for dimensions up to 8 (not studied for >8)
- Would be better suited for cases where difference is on most stages rather than on just 1 or 2

To judge the performance of these tests one must determine how consistently the test results agreed with the true answer. However, the true answer must be known, and this is not simple in the case of APSD profiles.

The PQRI Profile Comparisons Working Group developed a set of 55 different scenarios based on real product differences. As a basis for evaluation, the group members, who have much experience in CI testing and inhaled products, rendered their expert judgment on whether each scenario should be considered equivalent or not. Not unexpectedly, for many of the scenarios there was no clear agreement among the members. For each scenario, 1,000 sets of profiles

were generated, and the chi-square test applied. The distribution of the test results were then compared to the relative number of “equivalent” or “not equivalent” judgments by the working group members.

These same 1,000 sets of profiles for each of the 55 scenarios were also evaluated using the f2 and MVBE tests.

Statistical approaches conclusions

- All three approaches generally agree in rank order for the lower variability profiles
- MVBE may be more sensitive to differences in variability
- No approach seems to be able to consistently discriminate among differences likely to be of practical importance
- Difficult to evaluate performance when there is no clear consensus on “truth”

Quality by Design for Orally Inhaled Drug Products
Lawrence X. Yu, Ph.D. and Sau L. Lee, Ph.D., Food and Drug Administration

Pharmaceutical quality is defined as a drug product that is free of contamination and reproducibly delivers the therapeutic benefit promised in the label to the consumer.⁽⁵²⁾ The following equation indicates the basis of pharmaceutical quality:

$$\text{Pharmaceutical Quality} = f(\text{drug substance, excipients, manufacturing, and packaging}).$$

The above description of pharmaceutical quality implies that quality cannot be tested into products and must be built in by design. Thus, an understanding of how formulation and manufacturing process variables influence product quality is a prerequisite for enhancing quality.

Quality by Design (QbD) is a systematic approach to development that begins with predefined objectives and

emphasizes product and process understanding and process control, based on sound science and quality risk management.⁽⁵³⁾ It means designing and developing formulation and manufacturing processes to ensure a predefined quality. Design of experiments (DOE), risk assessment, and process analytical technology (PAT) are tools to implement QbD.

QbD should be utilized in the development of OIPs because (1) drug delivery to the lungs from these drug products depends on both formulation and device; (2) product handling may affect received dose; (3) manufacturing process of OIPs often exhibits a low process capability; (4) environmental effects may influence product manufacture and use; (5) testing efficiency of aerodynamic particle assessment methods is low, and (6) clear IVIVCs are lacking.

QbD essentially consists of the following four steps:⁽⁵⁴⁾

1. Define quality target product profile
2. Design and develop drug product and manufacturing processes
3. Identify critical material attributes, critical process parameters (CPPs), and sources of variability
4. Control manufacturing processes to produce consistent quality over time

Defining the quality target product profile is the first step of QbD. It is a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product.⁽¹⁰⁾ It is used to establish formulation strategy and keep the formulation and development effort focused and efficient. Considerations for the quality target product profile could include the intended use in a clinical setting, route of administration, dosage form and strength, container closure system, drug release or delivery, and attributes affecting PK characteristics as well as drug product quality criteria.

The quality target product profile for DPIs may include:

1. *In vitro* performance, including emitted dose, APSD, and delivered dose uniformity
2. Product stability and purity
3. Patient usability/acceptability
4. Local and systemic delivery, including PK and PD measurements

The second step of QbD is to design formulation, device, and manufacturing processes. The formulation of DPIs is relatively simple. It consists of micronized drug particles attached to large carriers such as lactose or micronized drug particles agglomerated into soft pellets. Formulation factors include drug and excipient particle size, shape, density, surface properties, and polymorphic form. These factors determine particle interactions (i.e., drug–drug, excipient–excipient, and drug–excipient interactions) that may influence fluidization and deaggregation of a dry powder formulation and hence respiratory drug delivery. Factors that need to be considered for device design include device resistance, device materials, and patient usability.

Identifying critical material attributes, process parameters, and sources of variability is the third step of QbD. The major purpose of this step is to establish relationships between critical material attributes/process parameters and critical quality attributes of a drug product. These relationships are ideally established based on the mechanistic understanding.

When such relationships are not possible, DOE can be used to establish empirical relationships. It should be pointed out that such empirical relationships do not need to be explicit mathematical or statistical equations.

Furthermore, because dry powder manufacturing processes involve numerous material attributes and process parameters, it is unrealistic to investigate each of these factors. To rationally select material attributes and process parameters that will likely have a significant impact on the quality of a drug product, a risk assessment should be used to reduce the number of material attributes and process parameters to be experimentally investigated. Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards. Risk identification is a systematic use of information to identify hazards related to the manufacturing process. Risk analysis is the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms. Risk evaluation compares the identified and analyzed risk against given risk criteria.

Design space is created during the studies of process identification and understanding. Design space is the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change, and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval.⁽¹⁰⁾ Despite its potential usefulness in simplifying a regulatory post approval change process, design space has met numerous challenges with respect to its establishment and regulatory approvals. For example, the design space is generally established at small scale. It is not yet possible to apply the design space established at small scale to commercial scale without actual verification at commercial scale. Because actual verification data are generally not submitted with regulatory applications, it is not possible for regulatory review scientists to fully approve the design space proposed by the applicant unless it has been verified or could be verified at commercial scale.

Controlling manufacturing processes to produce consistent quality over time is the last step of the QbD. Control strategy consists of three levels as shown below:

Level 1: Extensive end product testing + Fixed Critical Process Parameters (CPPs)
Level 2: Reduced end product testing + Flexible manufacturing process within fixed design space
Level 3: PAT, Real-time automatic "engineering control" + Flexible manufacturing process

Level 1 addresses variability by excessive testing. Level 2 addresses variability by limited testing and establishing design space for critical material attributes and process parameters. Level 3 is a robust process that can ensure quality in the presence of uncharacterized variability, and is therefore the best control strategy.

In summary, QbD means designing and developing formulation and manufacturing processes to ensure a predefined quality. It is the basis for science-based regulatory decisions, and applicants are strongly encouraged to share

Pharmaceutical Development information in the application with the Agency. QbD provides opportunities for applicants to develop high quality inhalation products.

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 that occurred in three separate breakout sessions. Inevitably this summary cannot contain all the detailed opinions that were so graciously shared.

In Vitro Approaches to Demonstrating Bioequivalence
 Facilitators: David Christopher, M.S., Schering-Plough,
 Richard N. Dalby, Ph.D., University of Maryland,
 Bing Li, Ph.D., U.S. Food and Drug Administration
 Scribes: Wallace P. Adams, Ph.D, U.S. Food and Drug
 Administration and Mei-Ling Chen, Ph.D., U.S. Food
 and Drug Administration

During this breakout session, we tried to elicit opinions on several topics. These were:

1. Which OIP *in vitro* testing methods are generally considered useful?
2. What are the challenges and barriers to the use of *in vitro* testing for the assessment of BE?
3. Are there opportunities to use new or modified *in vitro* tests to demonstrate BE?
4. Which *in vitro* tools would be useful for determining BE during development and what is needed to demonstrate an IVIVC or relationship for OIPs?

Interest in the first two topics was intense, and we did not get to discuss the issue of new methods or IVIVC in any substantial way. Perhaps these can be topics for a future workshop. Guided by participant interest, discussions focused on (1) general issues surrounding *in vitro* tests, (2) unit dose sampling apparatus and cascade impaction, and (3) spray pattern and plume geometry tests.

General issues. The audience generally agreed on several important points as described below.

The attendees agreed that resource issues associated with the conduct of specific analytical tests are a bigger consideration for Chemistry, Manufacturing, and Controls (CMC) (QC) tests compared to one-time BE tests. The attendees also agreed even though the same analytical tests (i.e., involving laboratory hardware) may be used in an *in vitro* BE or CMC (QC) setting, different statistical tests and limits may be used to evaluate the results of the analytical tests. This was viewed as appropriate because in the BE setting the T and R products are compared with the objective of detecting potential differences between the T and R products. In a CMC setting, analytical test results for a given batch are compared to a fixed specification.⁽⁵⁵⁾ Discussion of CMC testing was limited by the moderators because this was not the focus of this workshop, but test methods for BE are generally a subset of CMC tests so these discussions impact people working in both areas. Emphasis was made on the importance of con-

sistently making the “right” decision, which is different from a finding of “no statistical difference” between T and R products. For example, the Chi-square plus Impactor Sized Mass (ISM) test evaluated by the PQRI Profile Comparisons Working Group was not viewed as adequate for supporting a finding of BE because the test was not capable of detecting differences associated with nonequivalence.⁽⁶⁾ The goal should be declaring products to be bioequivalent when they are, and not bioequivalent when they are not. It was noted by one of the moderators that because there is no clear-cut consensus on the difference in APSD profile that can result in an important biological difference, other factors besides this test should probably be considered, and therefore, the final assessment of BE may involve an element of judgment and may not be a strictly statistics-based decision.

Generally, Population Bioequivalence (PBE) methodology that incorporates scaling of R product variability was regarded as a useful statistical evaluation tool for BE determination for the *in vitro* test comparison of OIP. The audience recognized that this approach differs from the Average Bioequivalence approach (ABE) which firms applied in the past on submissions to both European regulatory authorities and FDA. The draft FDA Nasal BA/BE Guidance⁽⁵⁶⁾ recommends statistical analysis of *in vitro* comparative data of a number of tests based on PBE.⁽⁵⁷⁾ It should be noted that although the 22 Jan 2009 EMEA Guidance on Clinical Documentation for OIP,⁽³⁰⁾ including Requirements for Demonstration of Therapeutic Equivalence, does not specifically recommend PBE, it is not prescriptive, and does not exclude the PBE approach. Participants pointed out that implementation of PBE might be challenging in some cases due to potentially large sample sizes of T and R needed for evaluation, and the practical difficulties associated with obtaining multiple batches of unexpired R product. Although for PK, PD, and clinical studies, a power analysis is commonly used to estimate how many subjects should be evaluated to have a reasonable expectation of achieving the necessary discriminating power, this is not typically done for *in vitro* tests. *In vitro* testing is usually approached with a predefined number of replicates. In the situation in which an adequately powered assessment of BE cannot be made with this number of replicates, whether ABE or PBE is employed, the audience asked if a sequential study design, in which additional replicates could be added would be acceptable, provided the alpha level (Type I error) is preserved. The answer was Yes, which is consistent with how some clinical studies are done. In practical terms, firms are advised to submit a protocol to FDA for comment and confirmation on the statistical approach prior to collecting data employing a sequential design.

The discussion also addressed the issue of using appropriate R batch samples in the *in vitro* tests to support BE. It was stated that R product batches may change over time. We discussed the practice of screening a range of R product batches to “preselect” those that generate results most closely matching the potency of the T product. The motivation to do this varied. Some did it to characterize the variability of the R product so they knew the target for product development and/or to choose batches that give results closest to the T product they had developed. We could not reach consensus on the appropriateness of using R products selected at random versus selecting R products determined to be closest in *in vitro* performance to T product batches.

We discussed the possibility of forming a consortium of generic companies that could collect and share data on several batches of a common R product. The intention would be to make an *in vitro* performance database available for use as a basis for formulating a generic product. In addition, this would avoid the current situation, in which only the regulatory agency may have access to multiple data sets on R products (and an individual firm would only know if their R data were “atypical” after incurring the expenses of a full regulatory submission). Some people thought it would be impossible to collect such pooled R product data in a pre-competitive way because there are large financial incentives to be the first approved generic.

A question that arose was whether resource issues justify testing fewer than three R batches. A related question was: “When the R variability is tight, is it acceptable to test fewer than 3 batches if this is sufficient to demonstrate statistical equivalence?” The audience referred to the draft FDA Nasal BA/BE guidance statistical information,⁽⁵⁷⁾ which recommends using 10 units from each of three batches of T and three batches of R product. The recommended three-batch approach was considered an appropriate minimum to obtain information about between-batch variability. The distinction between analytical variability and product variability was made, recognizing that the R product variability could not be modified by the generic applicant. With PBE, the T product is rewarded for lower variability. Some people were surprised to learn that there was no prohibition on looking at more than three batches. Some people asked if we should limit the number of *in vitro* test replicates to avoid “testing into compliance.” However, it was pointed out that when using an equivalence-based approach (PBE or ABE), an increased sample size increases the probability of making the “right” decision, not “testing into compliance.” With both statistical approaches, testing more batches does not increase the chance of falsely declaring inequivalent products to be bioequivalent.

There was an interesting conversation about blinding and bias. The goal was really thought to be avoidance of bias, rather than blinding. Several people suggested that their companies blinded all phases of BE data collection and evaluation, whereas others admitted that this was practically impossible because in many cases devices are physically different and even minor differences are readily distinguished by analysts. The group’s feeling was that blinding of sample collection is difficult or impossible, but that sample analysis (assay) can be partially blinded by use of a second analyst who did not conduct or witness dose release testing. The consensus was that actuation (dose release) could be automated to reduce operator bias, but that this necessitates careful selection, validation and justification of robotic actuation parameters to avoid introduction of different biases. Some people reported blinding of the statistical evaluation, but most people considered this unnecessary or even undesirable, especially if the statistical methods were decided before data collection, which best practices dictate should generally be the case. We noted that R products are potentially older than T product batches, which could introduce bias of a different type.

Another interesting conversation on which there was no consensus was the observation that labeled information on Emitted Dose is present for some R products, and could therefore be used as a target for comparison to a T product.

One such example cited was Advair[®], for which the Emitted Dose under standard test conditions (60 L/min/2 sec) occurs in the product labeling.⁽⁵⁸⁾

Unit dose sampling apparatus and cascade impaction. Use of the 4-kPa pressure drop was judged appropriate for setting test flow rates for use during *in vitro* testing of DPIs. We considered use of the same test flow (selected based on the 4-kPa pressure drop test described in the USP) rate for T and R DPIs so long as the resistance of the T DPI was within $\pm 10\%$ of the R DPI. Some people thought that both inhalers (T & R) should be tested at the specific flow rate defined by each inhaler’s resistance at a 4-kPa pressure drop, even if their resistances were only slightly different. A resource intensive alternative that was discussed involved evaluating the T DPI at the flow rate dictated by its resistance and that of the R inhaler (also dictated by its resistance), and vice versa. We could not reach a generally acceptable decision. It was noted that testing T and R inhalers at different flow rates dictated by specific resistance and 4-kPa pressure drop greatly complicates CI data interpretation and comparison because the cutoff diameters will be different for both sets of CI data. Fitting CI data to a model distribution would be a logical consequence of testing T and R products at different flow rates. Using the same CI stage groupings was also recognized as problematic if the T and R flow rates are not the same—particularly in the case where a product generates a lot of particles with a size approximating one of the CI stage cut-off diameters. Testing at one or more fixed flow rates (independent of device resistance) was also considered, and would be necessary if the innovator’s product labeling were the BE target.⁽⁵⁸⁾

There was little support for the idea of grouping DPI devices into “High,” “Medium,” or “Low” resistance groups, and using one or more test flow rates to evaluate all inhalers within a specific category. Defining category resistance boundaries was considered problematic inasmuch as an R device could exhibit a resistance close to the category boundary. An alternative approach was suggested whereby the T product would possess a resistance within a specified range from the R product resistance.

For solution products, it was generally agreed that spray weight and drug concentration in the bulk could be viable surrogates for emitted dose if validation regarding constant actuator losses and drug adsorption to the container were adequate. Aqueous solution nasal sprays are the obvious target for this approach.

The audience could reach no agreement of the appropriate simulated inhaled volume that should be used during emitted dose and CI testing, although many participants agreed that the impact of volume is likely to be highly sensitive to device design. The audience discussed the USP flow profiles imposed by the use of a timer-controlled solenoid valve,⁽⁵⁹⁾ and noted that fast opening of this valve generally produces a higher estimate of emitted dose and fine particle fraction (FPF) compared to use of more realistic breath profiles.⁽⁶⁰⁾ The same apparatus also renders the test relatively insensitive to DPI product performance compared to analogous tests when the valve is opened more slowly. We reached no agreement on the environment in which CI testing should be conducted. Some folks argued for testing at “lung humidity,” whereas others pointed out the analyst

revolt that might result from working at close to saturation water levels. Others argued for uncontrolled ambient conditions, because for a BE study it should be appropriate to mimic the patient use scenario as closely as possible.

Except for people who argued that only *in vivo* evaluation is adequate to support a finding of BE, the CI test was viewed as particularly useful in that it “captured” the results of other *in vitro* plume shape tests, which rendered such tests, at best repetitive and at worse uninformative and/or onerous. For example, some people wondered if emitted dose could be obtained by summation of drug recovery during CI evaluation. (However, in this case, the PQRI CI Mass Balance Working Group has determined that estimating emitted dose from CI determinations could introduce more variability.)⁽⁶¹⁾

Using multivariate PBE was discussed for assessing the equivalence of CI profiles. This approach provides an assessment of the CI profile as a whole, instead of separate statistical tests for groupings of stages. It was noted that there is evidence that, as with the chi-square approach, multivariate PBE lacks adequate discriminating ability to detect differences that are of practical importance. No multivariate test suitable for assessing equivalence of CI profiles has been identified at this time.

Spray pattern and plume geometry. Most participants appeared to agree that shape tests applied to pMDIs were not useful in BE or CMC (QC) assessment roles.⁽⁶²⁾ This is in contrast to shape tests for nasal sprays, for which some participants saw a useful role.⁽⁶³⁾ Only one individual who spoke up was a strong advocate for these tests for pMDIs. Some people thought that there was a role for spray pattern only for QC of incoming actuators associated with pressurized inhalers, but there was no reason to conduct the tests with anything other than propellant alone. It was thought that dimensional analysis (mensuration) of incoming actuators might be correlated to spray pattern, rendering the latter unnecessary if pursued as part of a QbD initiative. More people considered spray pattern and plume geometry tests potentially useful during pMDI product development activities.

The most widely expressed view held that product differences detectable by sheet laser or physical impaction would also be picked up by spraying into the inlet port of a CI. For example, if the spray pattern of a T product were wider or off-axis compared to the R product, this would result in more throat impaction, and/or alteration in the mass and distribution of mass among the stages of the CI. Because most participants recognized the necessity of conducting CI in both the BE and CMC arenas, spray pattern and plume geometry were considered duplicative ways to reach the same conclusion.

Spraying into the open atmosphere was not widely considered useful as a BE metric because it lacks patient relevance and is not consistent with simulating airflow through the inhaler during spraying. One person asserted that open atmosphere spraying made the test more sensitive.

Additional discussion points. One participant asked if anyone saw value in the “plume force test” during which a pressurized formulation is discharged into a target at a fixed distance away from the spray nozzle with the objective of recording the resulting force or force profile. The answer in

the only session that addressed this question was “no” as a BE metric, although one person thought it was useful during the chlorofluorocarbon (CFC) to hydrofluoroalkane (HFA) transition. It was noted that the study of particular instrumentation in FDA research does not imply agency endorsement of that technology.⁽⁶⁴⁾

Biomarker Strategies

*Facilitators: Richard C. Ahrens, M.D.,
University of Iowa, Dale P. Conner, Pharm.D.,
U.S. Food and Drug Administration and Partha Roy, Ph.D.,
U.S. Food and Drug Administration
Scribe: Kevin C. Fitzgerald, R.Ph.*

Background. The FDA defines BE as being present when two formulations are pharmaceutical equivalents whose rate and extent of absorption are not significantly different when administered to patients or subjects at the same molar dose under the same experimental conditions.⁽⁶⁵⁾ Demonstration of BE for topically administered drugs intended for local action, including orally inhaled drugs, has been challenging.

PK assessments are a necessary part of regulator submissions for new formulations of already marketed orally inhaled drugs. Comparison of the rate and extent of absorption of drug into the systemic circulation following administration of T and R formulations clearly provides important information concerning the relative risk of the two formulations for producing adverse systemic effects. However, these studies have not been considered to be sufficiently reflective of delivery of drug to the pulmonary biophase because (1) drug can reach the lung by absorption of being orally deposited from the gut (thus bypassing the lung), and because (2) even drug deposited in the lung can be absorbed both from the pulmonary biophase and sites not relevant to the beneficial clinical effects of the drug. Although the former can be dealt with by blocking gut absorption with activated charcoal, the latter remains a concern.

The alternative is to use a PD effect of the drug as a biomarker that reflects delivery of drug to the pulmonary biophase. A biomarker is defined as “a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.”⁽⁶⁶⁾ To be useful for evaluation of BE of orally inhaled drugs, the biomarker must be an indicator of a pharmacologic response that is exerted via the same site(s) of topical action in the lung as the desired therapeutic effect of the drug. It must also quantitatively reflect delivery to this pulmonary biophase and do so with sufficient precision to provide the statistical power necessary for assessment of BE of T and R formulations.

The biomarker, however, does not need to be one of the desired clinical effects of the drug. An example of this is the use of skin blanching as a biomarker for delivery of corticosteroid formulations intended for topical application on the skin. Following absorption into the skin, these agents have a local vasoconstrictive effect. Although the resultant blanching of the skin is not in itself a desired clinical effect of these topical corticosteroids, it does reflect delivery into the same region of the skin that is the site of the desired anti-inflammatory actions of these drugs. Quantitation of this skin blanching has been successfully used as a biomarker of

delivery of corticosteroid absorption into the skin and for assessment of BE of absorption of T and R formulations.⁽⁶⁷⁾

The only successful examples to date of use of PD response biomarkers to assess BE of orally inhaled drugs have been the evaluation of generic CFC–albuterol formulations relative to the innovator albuterol product, CFC-containing Ventolin. First attempts to accomplish this task used albuterol-induced improvements in lung function (FEV₁). This clinical study model had been used for assessing bronchodilators such as albuterol for more than 2 decades, but as typically carried out, these studies proved incapable of exhibiting a statistically significant dose–response in the range of clinically relevant doses. These types of studies were, therefore, not useful for assessment of BE. Simply stated, if a study cannot tell the difference between different doses of the same drug, it cannot hope to accurately detect differences in dose delivered by different formulations. This led to a search for methods that could detect a significant dose–response. The biomarker that first accomplished this was albuterol-induced inhibition of bronchoprovocation with histamine.⁽⁴⁰⁾ Bronchoprovocation with drugs that induce bronchoconstriction such as histamine or methacholine is widely used to measure the increased airway responsiveness that is characteristic of asthma. Bronchoprovocation with histamine and methacholine is quantitatively associated with both asthma symptoms and medication requirements.⁽⁶⁸⁾ In brief, these drugs are inhaled beginning at very low doses (e.g., 0.03 mg/mL of histamine or methacholine) and FEV₁ is subsequently measured. The concentration is then progressively increased (by sequentially doubling or quadrupling concentration) until the FEV₁ falls by >20% for baseline value. The concentration of drug that would produce exactly a 20% decrease is then estimated (PC₂₀FEV₁), where PC₂₀ is the provocative concentration of challenge agent causing a 20% fall in FEV₁. This serves as an indicator of the degree of airway responsiveness present—the lower the PC₂₀FEV₁, the greater the airway responsiveness. Patients with asthma have PC₂₀FEV₁s that are 10 to 1,000 times lower than normal subjects.

Clinically relevant doses of inhaled albuterol and related drugs can increase the PC₂₀FEV₁ in an individual subject by 10–20-fold, and this shift is highly correlated with the dose administered (i.e., a highly significant dose–response relationship is present). This allows the dose–response curve for the R formulation to be, in essence, used as a standard curve against which the T formulation is compared. This leads to an estimate of the clinical potency of the T formulation relative to the R. A confidence interval is placed on this estimate, and this is compared to the FDA-determined BE limits. If the entire 90% confidence interval lies within these limits, the T formulation is deemed to be bioequivalent to the R formulation. Specifically, each microgram of a generic formulation produced by Baker Norton was estimated to be equivalent to 1.01 mg of CFC Ventolin [90% confidence interval (CI) 0.69–1.50].⁽⁴⁰⁾ This confidence interval fell entirely within BE limits of 0.67 to 1.50 that were deemed acceptable by the FDA. This approach has been used subsequently with another outcome measure biomarker (carefully designed studies of improvement in FEV₁)⁽⁶⁹⁾ and to support NDA applications as well as generic ANDA applications.⁽³⁹⁾

Multiple statistical approaches to fitting the dose–response curve and establishing the estimate of relative clinical po-

tency have been used, but the FDA currently favors use of E_{max} modeling for curve fitting and estimation of relative clinical potency and bootstrap methods for establishing the confidence interval (“dose-scale analysis”).

An important problem for extending this approach to other drug classes used to treat asthma is that clinically used doses appear to lie near the top of the dose–response curve for many biomarker outcome measures, making it difficult to establish the highly significant dose–response relationships that are essential for use of PD biomarkers in assessment of BE. This is particularly true for ICS used in the treatment of asthma.

Points of consensus. There was wide agreement concerning the following.

As described above, use of PD biomarkers for assessment of BE for SABAs such as albuterol for the treatment of asthma is well established. These methods will likely continue to be useful for assessment of BE of these agents.

Use of similar methods for evaluation of BE of LABA formulations (e.g., salmeterol and formoterol) is likely to be successful. In particular, LABAs are able to shift airway responsiveness in a fashion similar to albuterol.⁽⁷⁰⁾ However, some modifications will be needed when designing BE studies for this purpose. Specific attention will need to be directed to a longer length of time to reach peak effect of these long-acting agents, and to determination of the appropriate sample size. The later may not be the same as is required for SABAs.

For all classes of orally inhaled drugs, BE studies will need to use crossover rather than parallel study designs. Otherwise, it is unlikely that sufficient statistical power will be achieved to accomplish the task of proving BE.

Open issues. The following unresolved issues were raised during the discussion.

It is unclear whether BE studies for LABAs will need to address duration of action as well as peak effect of these agents. If this is required, study designs will need to be modified accordingly.

One of the greatest problems facing the use of biomarkers for assessment of BE of orally inhaled drugs is the choice of a suitable biomarker strategy for evaluation of ICS formulations in patients with asthma. Because the dose–response appears to be relatively flat in many patients with asthma, typical studies comparing ICS doses have been unable to identify a statistically significant difference between administered doses. Although most of these studies have used parallel study designs, use of a crossover study design is an essential part of maximizing power to identify dose–response and evaluate ICS BE. Other strategies to maximize power were discussed during this session. The first is selection of a biomarker that lies close to the linear, rising portion of the dose–response curve. Candidates for this role include measurement of eNO,^(10,51) the stability of an asthma model,^(71,72) measurement eosinophilia in induced sputum samples (which has been adopted by Canadian regulatory authorities),^(34,73) and bronchoprovocation with adenosine.⁽⁷⁴⁾ It is clear that each of these outcome measures is significantly affected by ICS in comparison to placebo. It is less clear which of these measures will be best able to show highly significant differences in effect between clinically approved doses of ICS

formulations. Available data suggest that the stability of an asthma model may be suitable for demonstrating BE.⁽⁷²⁾ Disadvantages of this model are that a relatively large number of subjects need to be screened in order to identify an appropriate study population, and the long duration of study participation for each subject. Each of the other biomarker outcomes appear to hold promise, but require additional investigation. The second strategy is to enrich the study population with individual patients who are most capable of showing a significant dose-response. This needs to be accomplished during study screening procedures, using tests to identify "good responders." A third strategy proposed during this session is the administration of approved doses of the ICS at longer than recommended dosing intervals. For example, recommended doses of fluticasone could be administered once rather than twice daily, in hopes of moving further down toward the linear portion of the dose-response relationship and thereby increasing statistical power.

It is unclear what BE limits will be required for orally inhaled drugs in the future. BE limits for orally administered agents that exert their therapeutic effect following systemic absorption mandate that the T formulation be demonstrated to deliver between 0.80 and 1.25 times as much drug to the systemic circulation as R formulation. However, clinically based arguments have been made that BE limits for orally inhaled drugs should be wider.⁽⁷⁵⁾ The precedent set during approval of generic CFC-containing albuterol metered dose inhalers during the 1990s is in accord with this.

Interest was expressed in the possibility of relying solely on PK measures for assessment of BE of orally inhaled drugs, particularly corticosteroids. It was agreed that this will require further evaluation and validation before it could be adopted.

BE of orally inhaled drugs used for treatment of COPD was not extensively discussed. However, the following questions were raised: for orally inhaled drugs that are used both in the treatment of asthma and COPD, is demonstration of BE of two pharmaceutically equivalent formulations in patients with asthma sufficient for assumption of their BE in treatment of COPD? Is it conceivable that two formulations could be bioequivalent for treatment of asthma and yet be inequivalent for treatment of COPD?

It is clear that additional research is needed for investigation and validation of methods to be used in assessing BE of orally inhaled drugs. However, ability of the FDA to fund this work is limited. There was lack of consensus concerning what other funding sources might be made available.

Imaging Techniques

Facilitators: Beth L. Laube, Ph.D., Johns Hopkins University School of Medicine, Sau L. Lee, Ph.D., U.S. Food and Drug Administration, Anthony J. Hickey, Ph.D., University of North Carolina

Scribes: Gary R. Pitcairn, Ph.D., Pfizer, and Julie D. Suman, Ph.D., Next Breath, LLC

Introduction. Inhalation aerosols are routinely characterized using CI. However, the relationship between CI data and the amount of drug actually reaching the lungs is poorly understood. Imaging techniques can be used to measure how much drug is delivered to the lungs from an inhaler. The data from imaging studies can therefore be considered to

be a bridge between *in vitro* and *in vivo* data. The objective of this breakout session was to explore the potential of using imaging studies to assess BE between inhaled drug products.

Breakout sessions. In each breakout session, information about various aspects of using imaging techniques to assess pulmonary drug delivery was presented. This information was used to frame a series of questions that were used to elicit opinions from the participants, who included representatives from industry, academia, and the regulatory authorities. The questions posed were:

1. Can CI data be used to predict either the amount of drug deposited in the lungs or the site of deposition within the lungs?
2. Can radionuclide imaging be used to quantify *in vivo* lung deposition of inhaled drugs?
3. Can radionuclide imaging be used to measure the regional lung distribution of an inhaled drug?
4. Can inhaled drug products be radiolabeled such that the aerosol performance is essentially unchanged?
5. Can imaging be used to assess BE of inhaled drug products?
6. Can *in silico* modeling play a role in establishing BE?

Responses to the above questions are summarized below.

1. *Can CI data be used to predict either the amount of drug deposited in the lungs or the site of deposition within the lungs?* Marketing presentations for some CI systems suggest that there is a direct relationship between drug deposition in specific airways and the particle cutoff diameter of each impactor stage. These claims were discussed and it was agreed that given the fact that the CI separates small particles from large particles based upon inertial impaction, the data should have some relevance to how much aerosol will reach the lungs. However, we do not have a well-understood model that correlates impactor data with regional lung deposition of inhaled drugs. Consequently, the CI was generally considered to be a QC tool.

Some reasons for the lack of an *IVIVC* were agreed upon:

- Air velocity in an impactor increases as it passes through the various stages; whereas in the lung, air velocity actually decreases due to the increasing number of airway generations and cross-sectional area.
- The inlet port (throat) does not represent the complexity of patients' upper airways or account for device-patient interactions.
- During CI testing, a vacuum pump draws air continuously from the inhaler. This does not reflect the inhalation pattern of how patients inhale through the device.

In a recent article by Newman and Chan,⁽²²⁾ the authors correlated *in vivo* whole lung deposition data from published scintigraphy studies with FPF data. A range of inhaler types were used in the studies included. The authors showed that there was a correlation between the *in vivo* whole lung deposition data and the *in vitro* FPF provided the latter was expressed as a percentage of the dose less than 3 μm .

It was agreed that this was an interesting article, but as there were no statistics presented around the mean data, the

correlation should be considered more of a broad relationship. The data presented in this article suggest that CI data may be used to estimate average lung deposition for an inhalation device, but cannot provide data on the intersubject variability in lung deposition.

In the context of assessing BE, people commented that the site of action of a drug within the lungs needs to be considered as well as the amount of an inhaled drug that reaches the lungs. It was agreed that the impactor stages do not represent specific human airways, and so CI data may not be used to assess quantitatively where the drug will be deposited within the lungs.

It was concluded that it may be possible to use CI data to estimate the overall percent lung deposition, but the data cannot be used to predict deposition percentages within regions of the lungs.

2. *Can radionuclide imaging be used to quantify in vivo lung deposition of inhaled drugs?* Whole lung and regional lung deposition of inhaled asthma drugs can be quantified using either two-dimensional (gamma scintigraphy) or three-dimensional (SPECT and PET) radionuclide imaging methods.⁽⁷⁶⁾ The 2D method of gamma scintigraphy has been used extensively to assess pulmonary drug delivery, and is considered the industry standard.⁽⁷⁷⁾ It was accepted by the workshop participants that gamma scintigraphy is a well-established method of evaluating pulmonary drug delivery from DPIs, pMDIs, and nebulizers.

There was considerable discussion around the choice of using 2D or 3D imaging techniques. The following points were discussed, and it was agreed that these factors need to be considered when selecting an imaging modality:

- Choice of radiopharmaceutical used to radiolabel the drug
- Time required to acquire all the necessary images
- Amount of radioactivity required

It typically takes 2 to 3 min to acquire 2D images to quantify deposition. SPECT imaging typically takes longer (~15–20 min), but this can be reduced by using triple-headed cameras. Given that SPECT images take longer to acquire, SPECT is considered more technically challenging due to the potential for the radiopharmaceutical to be cleared from the lungs by either systemic absorption or mucociliary clearance during the imaging procedure. In addition, SPECT studies require a higher dose of radioactivity to improve the signal-to-noise ratio. Consequently, 2D imaging was seen as the more likely choice for measuring lung deposition with a view to assessing BE.

PET was considered an inappropriate imaging modality for assessing BE due to the need to incorporate a positron emitting nucleotide into the molecule, manufacture the radiolabeled formulation, and then fill/assemble the inhaler. The main concerns were the perceived difficulty of demonstrating that the innovator product was unchanged by this process and the time and cost of conducting such a technically complex study.

It was concluded that radionuclide imaging can be used to quantify *in vivo* lung deposition, but in order to understand how a product performs *in vivo*, measurements of *both* whole lung and regional lung deposition are necessary.

3. *Can radionuclide imaging be used to measure the regional lung distribution of an inhaled drug?* The workshop participants were shown images of the same aerosol deposited in the lungs of a healthy volunteer and in the lungs of a patient with severe asthma. The images clearly showed a profound difference in regional lung deposition, and emphasized the importance of measuring both whole-lung and regional deposition.

It was recognized that planar lung images (obtained by 2D imaging techniques) can be analyzed to quantify how much drug reaches different regions of the lungs. One method used by investigators involves characterizing the lungs into central and peripheral lung regions, to represent the large and smaller airways, respectively.

However, the drawback of this approach is that each 2D lung region is likely to contain both large and small airways due to the 3D nature of the lungs. This limits how well data from gamma scintigraphy studies describe drug deposition in specific airways. Despite this limitation, regional lung deposition data generated in this manner have been shown to be capable of discriminating between aerosol particle size, inhalation flow, and degree of airway obstruction.⁽⁷⁸⁾

It was concluded that radionuclide imaging can be used to measure the distribution of drug within the lungs. However, concern was expressed that the definition of what constitutes central and peripheral lung varies between laboratories. It was agreed that the methodology needs to be standardized to permit comparison of data across laboratories and to determine the inherent variability of the measurement.

4. *Can inhaled drug products be radiolabeled such that the aerosol performance is essentially unchanged?* It was recognized that prior to conducting any experiments with a radiolabeled aerosol, it is first necessary to develop a small-scale, extemporaneous method of manufacturing the formulation and device to be investigated. Then, the *in vitro* performance of an inhaled drug product made in this manner must be comparable to the *in vitro* performance of drug generated by the industry manufactured device. This is a significant technical hurdle that is frequently overlooked.

Then, the *in vitro* performance of the radiolabeled aerosol must be comparable to the *in vitro* performance of the unlabeled aerosol. The accepted method for validation is to compare the APSD of unlabeled drug to the APSD of both the labeled drug and the radiolabel.⁽⁷⁹⁾ If the APSD of unlabeled drug and labeled drug match, this indicates that the radiolabeling process has not adversely affected the drug product. If the APSD of unlabeled drug and radiolabel match, this indicates that the radiolabel will act as a valid *in vivo* marker for the drug.

It is relatively easy to radiolabel solution formulations. Radiolabeling suspensions and dry powder formulations is more challenging, and it is generally harder to demonstrate that the product is unaltered and that the radiolabel accurately reflects the drug distribution.

Mismatches between the APSD of the unlabeled drug, labeled drug, and radiolabel can occur, but when is a match unacceptable? No consensus was reached. Historically, if the ratio of the FPF of the radiolabeled drug to the FPF of the unlabeled drug is between 0.8 and 1.2, the radiolabeling method is deemed suitable for estimating whole deposition of the drug.⁽⁸⁰⁾

It was concluded that it is possible to radiolabel some products such that the aerosol performance is essentially unchanged, but this can be technically challenging and is very much formulation- and device-dependent. This can only be achieved by validating each formulation and device combination as stated in the literature.⁽⁸⁰⁾

5. *Can imaging be used to assess BE of inhaled drug products?* The majority of the discussion around this question involved the requirement to radiolabel both generic and innovator products. Provided the necessary device and formulation components could be acquired, the radiolabeling method would need to be validated such that the performance of the generic product could be shown to be indistinguishable from that of the innovator product.

The workshop participants agreed that it may be possible to radiolabel a formulation if you have access to all the formulation components, manufacturing processes, and empty devices. However, it is unlikely this will be the case for a generic versus innovator study.

For example, if you wish to radiolabel a marketed DPI product you would need to identify a source for micronized active pharmaceutical ingredient (API) that matched the innovator's specification, radiolabel it, blend this with excipients that again match the innovator's specification, and fill the device with the same degree of accuracy as the innovator's filling process. The workshop anticipated that these issues would be difficult to resolve without the innovator's help, which is unlikely to be forthcoming.

A similar problem is likely to exist for pMDIs in terms of obtaining the correct canisters and metering valves, and then filling and sealing canisters with radiolabeled formulation.

Following these discussions, workshop participants concluded that for an in-house development program where a company wants to demonstrate that changes to a formulation or device will not have an impact on safety or efficacy (i.e., bridging studies), imaging could be used to demonstrate that the old and new formulations/devices were bioequivalent, provided that the radiolabeling validation had negligible impact on product performance.

However, to establish BE between innovator and generic products, the issue of being able to radiolabel the innovator product was considered such a formidable barrier that imaging was *not* considered a viable option for demonstrating BE for an abbreviated new drug application (ANDA).

In the event that a company wanted to conduct an in-house study, the workshop participants agreed that BE could not be established solely on the basis of comparable lung deposition data. A "weight-of-evidence" approach should be adopted and additional data would be required.

The question of whether you should use HVs or patients in imaging studies was asked, and after some discussion, it was agreed that regional lung deposition would probably be less variable in HVs than in patients. Therefore, studies of deposition in HVs may be more discriminatory in terms of detecting differences between products. It was noted that studies in HVs would also likely permit a more manageable number of subjects to be used and therefore be more practical.

It was recognized that there is a need to define how BE should be established. Is a 90% CI achievable with a manageable number of subjects? It was felt that this was probably

not the case. However, a consensus on what criteria could be used to assess BE was not reached.

Additional questions were asked:

- What differences in the indices of deposition are clinically relevant?
- Do we need to have indices that are clinically relevant?
- Would it be enough to demonstrate equivalent whole-lung delivery and regional distribution within the lung in a bridging study?

It was agreed that these issues require further discussion.

6. *Can in silico modeling play a role in establishing BE?* Although *in silico* modeling is not an imaging technique, it was recognized that data from imaging studies have been used, or may be used to develop and validate such models. Given some of the issues identified with using imaging studies to assess BE, there was a brief discussion around whether *in silico* modeling might be an alternative method. Various questions were posed:

- How discriminating is this modeling technique in terms of simulating disease populations?
- How discriminating is this modeling technique in terms of simulating breathing patterns and flow rate?
- What factors other than APSD are included in the model?
- What parameters are included in the model?
- How does the model account for device-patient interactions?

It was felt by some of the participants that models with a physiological basis may be useful in terms of establishing trends. It was generally agreed that *in silico* models can be useful in predicting drug absorption for orally administered drug products. However, not much work has been done with inhaled drug products. There was a consensus that *in silico* modeling may be helpful in the development of new inhaled drug products, but not useful in the BE assessment.

Session 3 summary. Imaging is a useful tool for assessing total and regional lung deposition of inhalation products. However, in terms of assessing BE of inhaled products, imaging is probably only useful for conducting in-house bridging studies, due to the problems associated with radiolabeling the innovator product. Further discussion is required regarding the clinically and statistically relevant criteria that should be applied to demonstrate BE. The workshop identified a need to standardize how regional lung deposition is quantified.

In Vivo Approaches to Establishing Local Delivery Equivalence

Facilitators: Gur Jai Pal Singh, Ph.D., Watson Pharmaceuticals, Leslie Hendeles, Pharm.D., University of Florida, Badrul A. Chowdhury, M.D., Ph.D., U.S. Food and Drug Administration, and Sandra Suarez Sharp, Ph.D., U.S. Food and Drug Administration
Scribe: Svetlana Lyapustina, Ph.D.

BE of the conventional dosage forms intended for systemic delivery is based on *in vivo* PK studies supported by

comparative *in vitro* dissolution data. However, it is believed that PK studies may not be sufficient for documentation of the locally acting drug products,⁽⁵⁶⁾ because delivery to the target sites of these drugs does not depend upon systemic circulation. Following administration of the locally acting OIP, drug moieties detected in the systemic circulation (1) appear subsequent to its delivery to and absorption from the local site, and (2) contain drug absorbed from multiple sites including the lung, buccal, and GI tract areas. Consequently, the OIP constitute a unique class of drug products and, according to current thinking, warrant special consideration for a comprehensive approach for determination of BE. Thus, based on the available information^(81,82) the FDA currently determines OIP BE using a “weight-of-evidence” approach, which includes evidence for equivalence of systemic exposure and drug delivery to the local site of action.

Due to the above-mentioned limitations of the PK BE studies in determination of equivalence in local delivery, the facilitators of this session initially focused on two other approaches, (1) *in vivo* testing in humans of an acute pharmacological effect and (2) controlled clinical trials in humans to establish safety and efficacy, listed among methods for documentation of BE in 21 CFR 320.24(b). To initiate the discussion the facilitators presented a list of factors that are currently considered in the design of the PD BE studies, including available *in vivo* models. The recognized models included FEV₁ (standard bronchodilation and nocturnal asthma), Methacholine Challenge (bronchoprotection) for bronchodilator drugs, and FEV₁ (Asthma Stability Model), Adenosine Challenge (bronchoprotection), eNO, and Sputum Eosinophils for corticosteroid drug products. Topics to facilitate discussion on study design included Subject Population (mild, moderate, or severe asthmatics), Placebo (availability and application), Study Duration, Study design (parallel vs. crossover, double dummy, triple dummy, etc.), and Dose–Response (necessity and possibility, clinical endpoint dependency, implication of the recommended dosing regimen, and definition of acceptable dose–response). Points for discussion also included Multistrength Products (possibility for waiver of *in vivo* testing for lower strengths) and Combination Products (PK and PD/clinical evaluations based on measurements of joint or separate effects). The facilitators also presented slides from Dr. Hendeles’ unpublished work on the albuterol dose–response study using the nocturnal asthma model and a pilot methacholine challenge study on the Foradil (formoterol) DPI. In the former, bronchodilator response was significantly greater when albuterol was delivered by an MDI than by DPI. In the latter study, there was no significant difference in bronchodilator response between 12 and 24 μg of formoterol in a crossover design of subjects with mild asthma (baseline FEV₁ \geq 70% predicted). In contrast, the methacholine PC₂₀ was significantly increased, an average of twofold greater, after a 24- μg dose compared to a 12- μg dose. These data indicate that additional developmental work with use of methacholine bronchoprovocation as a clinical bioassay for determining BE of the LABAs would be worth undertaking.

Due to the time constraints of each breakout session, and the interests of participants, all topics listed above could not be addressed adequately. The following were the principal topics of discussion.

Systemic exposure studies for assessment of equivalent local delivery. Due to the potential limitations of PK studies in determination of local delivery, the facilitators had planned to focus on the PD or clinical endpoints studies. However, in light of a relevant presentation⁽⁸³⁾ and the interest expressed by many participants, a significant portion of the discussion periods was spent on the possibility of using comparative systemic exposure (PK) studies, along with *in vitro* performance studies, as the sole indicator of *in vivo* BE of OIP. Briefly the presentation emphasized that for corticosteroids with no or negligible oral BA, measurements of drug concentration in the systemic circulation together with *in vitro* studies may provide sufficient information on the pulmonary fate of OIP (pulmonary available dose, central/peripheral deposition ratio, and pulmonary residence time) to support equivalence in drug delivery to the lung. It was recognized that the PK approach would need to be validated in clinical studies, but has the potential for being more sensitive. During the discussion it was emphasized that for drugs with measurable oral BA, studies of relative BA in subjects administered with activated charcoal before drug inhalation may be used to determine drug delivery to the lung. However, concerns were expressed regarding the integrity of the charcoal block for complete blockage of drug absorption from the GI tract, and a systemic contribution due to drug absorption from the buccal cavity soon after inhalation. It was also argued that although the charcoal block method has been used to study PK of some inhaled drugs, the methodology needs to be validated for each drug with respect to blockage of non-pulmonary absorption. Based on this approach studies without charcoal block can be used for determination of equivalence of total exposure and studies with the charcoal block supposedly would provide evidence for the equivalence of local delivery. The suggested approach for establishment of BE based solely on PK studies would be applicable to both single entity and combination drug products containing more than one active drug.

The charcoal blocking technique has been described by Borgstrom.⁽⁸⁴⁾ It has been used in exploratory studies for a variety of drugs.^(85–89) However, it has not been used to establish BE and support regulatory approval of OIP by the FDA. It was discussed that if satisfactory validation for the charcoal block method could be achieved, would the evaluations with and without charcoal block be sufficient for establishment of *in vivo* BE of OIP? Some participants suggested that, when combined with comparative *in vitro* performance data, PK studies with and without charcoal could provide sufficient evidence for BE of OIP. However, there was no general agreement due to the apparent lack of information to support this viewpoint.

During the second round of this breakout session, validation of the charcoal block method was discussed. It was suggested that in addition to the oral administration of activated charcoal before and after aerosol administration, an oral rinse with activated charcoal can be used to prevent delivery from the buccal cavity. The efficiency of the charcoal’s binding depends on the drug (e.g., fluticasone is bound by charcoal better than budesonide). Therefore, the method should be validated for each molecule, and should also be validated *in vivo* because *in vitro* validation results may be unreliable. Overall, this PK approach to local delivery equivalence was found intriguing; however, more in-

formation is needed before one can consider this approach as the sole indicator of *in vivo* BE of OIP.

Goal posts. Conventional BE studies are found acceptable if the 90% CIs comparing the T and R products fall within the acceptable range of 80–125%. Some participants explored the possibility of different goal posts for OIP. It was emphasized that the goal posts of 80–125% for PK are generally accepted across dosage forms and are not likely to change for OIP. Some participants then inquired about the possibility of calculating the PD BE limits that would correspond to the 80–125% PK goal posts. For example, what would be the PD BE limits for the T/R ratio corresponding to the PK BE 80–125% limits? Furthermore, it was inquired what would be the PK limits corresponding to the 67–150% PD BE limits used for the approval of generic albuterol CFC MDIs in the 1990s? However, it was mentioned that consideration for such extrapolations is complicated by differences between the PK and PD data with respect to linearity in dose–response, differences in variability of measurements, and lack of recognized relationship between the two endpoints. Furthermore, the approach will require sophisticated mathematical modeling, and the basic data required for such modeling is not available in the public domain. Historically, however, the OGD has not used model driven data for determination of BE.

PD studies and dose–response. The FDA has previously relied on PD studies to establish equivalence of local delivery. It has accepted both bronchodilation and bronchoprovocation (methacholine and histamine challenge) studies for evaluation of BE of albuterol MDIs. It is important that the PD measure permit objective quantitation of responses. Therefore, an important feature of the PD BE studies is the ability to demonstrate a dose–response relationship. There was general agreement that demonstration of dose–response was essential because the steepness of the dose–response relationship, along with variability, determines the ability of a bioassay to distinguish between the single- and multiple-actuation doses of a drug product. It was also acknowledged that the dose–response is influenced by a number of factors including the study drug, biomarker, disease severity, and precision and sensitivity of measurements. Discussion on PD studies also emphasized the significance of choosing PD endpoints that lend to objective quantitation. Determination of BE based on the PD studies may require comparison of the T and R products in terms of potency. In the past, Finney analysis has been used to estimate comparative potency. However, this method assumes linearity between the responses of single and multiple actuations, whereas the PD responses are generally nonlinear. Therefore, the FDA has previously used the E_{max} model.⁽⁹⁰⁾ It was mentioned that limited (unpublished) data analysis based on the Finney method and the E_{max} model yielded similar results.

Exhaled nitric oxide. The symposium talk given by Badrul Chowdhury⁽⁹¹⁾ indicated the FDA's exploration of possible use of eNO as a biomarker in determination of local delivery from OIP containing corticosteroids. During the group discussion it was emphasized that it may be the best available model as eNO responds to steroids but not

to beta-agonists, and might allow objective quantitation of response. The method for measurement of eNO is ATS-standardized,⁽⁹²⁾ and an FDA-cleared instrument⁽⁹³⁾ is available for quantitation of eNO.

Despite these advantages, it was acknowledged that the currently available information on the eNO bioassay may be insufficient for the development of BE study protocols. It was expressed that previous dose–response studies^(10,12) mostly distinguished between a multifold difference in the ICS dose, and the presented data⁽⁹¹⁾ referred to limited evidence⁽¹¹⁾ to support the capability of this biomarker to distinguish a twofold difference in dose. In this regard, it was pointed out by a facilitator that the evidence presented at this meeting was indicative of possible use of the eNO bioassay for obtaining a meaningful dose–response. However, because of the noted limitations of the published studies, further exploratory work is warranted. It was noted⁽⁹¹⁾ that the FDA has sponsored a study to gain insights relevant to design of BE studies based on the eNO bioassay.

Subject populations. A part of the discussion in this breakout session was also focused on the subject populations. For the PK BE evaluations of the solid oral dosage forms the OGD relies on studies conducted in HVs, regardless of the modes of action and indications for drug use. It also relies on the use of HVs for determination of equivalence of systemic exposure from respiratory drugs.⁽⁵⁶⁾ It was argued that for OIP the HVs may provide better sensitivity and discrimination for safety studies (in part due to a higher exposure compared to patients). It was considered that PK results could be different between HVs and patients, but PK results should be the same between two equivalent drugs (e.g., a generic and an innovator) within the same subject population. Furthermore, the sensitivity of PK studies and their ability to detect differences in AUC and central-to-peripheral (C/P) lung deposition ratio would be the highest in HVs.

A question was raised that if a BE study is conducted using a very specific PD model in a very specific subgroup of patients, how can it be generalized to all patients under all conditions? In this regard, it was emphasized that asthma is a heterogeneous disease even in the same individual. When the purpose of the study is demonstrating BE, choosing the study design that can give the best discrimination is important. For new drugs, by contrast, studying all relevant patient populations is necessary. But for BE determination for a drug product with more than one labeled indication, the Agency may recommend establishing BE based on only one indication when the mechanism of action of the drug remains the same across the indications.

Drug delivery from most DPIs is dependent on the patient's inspiratory flow rate. Based on the available information, both the emitted dose and the APSD may be influenced by the flow rate through the DPI device.⁽⁹⁴⁾ In addition, the flow rate dependency of drug delivery from DPIs may influence their *in vivo* performance.^(95–97) Therefore, a question was raised if the BE study populations should encompass the entire range of target populations. It was considered that as long as *in vitro* data on a range of flow rates are available, studying the entire range of populations should not be necessary.

Combination drug products. For combination drugs that contain a beta-agonist and a corticosteroid, it may be difficult to show equivalence for both components with a single model⁽⁷¹⁾ that evaluates ICS monotherapy and does not separate the effect of two components. It was considered that BE studies for each of the two component drugs may need different types of patients, biomarkers, and different study designs. For example, testing salmeterol effects in Advair may require a patient population different from that suitable for testing the steroid effects.

Device Design Similarity

*Facilitators: Neil H. Parikh, Axar Pharma, David A. Parkins, Ph.D., GlaxoSmithKline and Prasad Peri, Ph.D., U.S. Food and Drug Administration
Scribe: Paul Lucas, Ph.D.*

Introduction. When considering the BE of inhaled products, it is necessary to take into account both device design and the formulation that is being delivered. Consideration also needs to be given to the interaction between the patient and device, as this is widely understood to influence *in vivo* drug delivery. There is therefore much debate as to what is meant by “device sameness,” when considered in the context of inhaled product BE. This subject is of interest to both the generic manufacturer, who may be prevented from marketing the same device as the innovator due to intellectual property concerns, and to the innovator manufacturer where changes in device design may occur during development. The key question that needs to be addressed when differences do arise between inhalers is “which ones are of practical and scientific relevance?”

The impact of device design and patient interaction was illustrated by Dr. Parkins, who reviewed the types of differences that may arise between inhalers, as well as a recently published case study.⁽²⁴⁾

The case study exemplified the importance of understanding the impact of device differences when considering inhaled product BE. As this subject is a key area that needs to be understood when considering criteria for inhaled product BE, it was selected as a specific topic for further discussion by the workshop attendees.

Discussion points. To facilitate the discussion on the subject of device design similarity the following questions were posed for discussion:

1. What is necessary to demonstrate device sameness in the hands of the patient, and what are the criteria for establishing similarity of operating principle and design for inhaled devices?
2. What is the role of *in vitro* testing in determining device comparability? What are the opportunities for using methods beyond cascade impaction and when comparing devices, what is considered to be comparable aerosol performance?
3. What considerations are necessary when demonstrating device sameness across different patient populations, for example, from adults to pediatrics, or from asthmatics to COPD patients?

Key to the discussion were the questions as to what was meant by device similarity and just how similar did devices actually need to be to be considered to be equivalent.

In the context of BE regulations, a number of questions raised by the participants, regarding the equivalence of innovator and generic devices, generated lively discussion. However, no consensus could be reached by the group, indicating the need for guidance in the area. For example, did the instructions and label of a generic device have to be identical to the innovator, and what (if any) constituted an acceptable difference? Similarly, what was the position when the generic device represented an improvement over the innovator device? Examples provided included a dose counter on the generic product, when the innovator did not have such a feature, and where a generic pMDI may require only two primes versus four primes for the innovator. In these cases a number of individuals commented that not allowing such improvements to a large extent stifled innovation as the innovator product would be an older product, whereas the generic could incorporate current technology. It was also commented that if the requirement for pharmaceutical equivalence, a basic tenet of the BE regulations, required the device to be identical, would it ever be feasible for a DPI to be approved by the ANDA route?

For example, did it really matter if device shape were different, or if there were a difference in operating principle, particularly if that difference were invisible to the patient? From the discussion, it was clear that there was a wide range of device differences that needed to be considered. Examples of these included a change in plastic supplier for an existing device, a change to a device that might impact its handling (e.g., addition of a button to facilitate opening of the device) and a comparison of two devices with a completely different metering principle and design (e.g., premetered vs. device metered). The diversity and range of such potential device differences makes it unlikely that any single-standard set of device differences could be defined, and their impact assessed and incorporated into an inclusive guidance. However, some clarity in this area would be welcomed, particularly to the extent of device similarity required to achieve pharmaceutical equivalence.

The importance of understanding how any device difference might result in a change in the way the device is used by the patient was discussed. Areas identified for consideration included differences that might impact the effectiveness of the inhalation maneuver (e.g., through impacting patient coordination) and differences that might change patient perception of whether they have received the dose (e.g., differences in mouth feel or audible feedback), which could potentially impact patient compliance. Some of these differences might be addressed through patient user studies, but consideration needs to be given when extrapolating data generated from one patient group to another patient population. For example, if the first group were teenagers with asthma, potential dexterity problems that might be experienced by an older patient group in a different disease population such as COPD would not be detected.

Consideration was also given to the practical patient experience that occurs when a device that is not identical is substituted at the pharmacy level. Such a device may require different operations for use, and be prone to different types and rates of critical errors. Will the patients receive adequate training, and what would be the impact on a patient who could potentially be receiving a different device on each visit to the pharmacy? In addition to the patient, the ability of

physicians, nurses, and pharmacists to ensure adequate training as devices are substituted needs to be considered. Levels of training and instructions provided by the health-care provider are not consistent across the world. Interestingly, Dr. Dale Conner stated in the final session that in his personal view a patient should be able to pick up a prescription for which a generic inhaler has been substituted and to be able to use it without additional instruction.

A risk management approach. From the diversity of opinions expressed during the breakout discussions, it was clear that a single set of criteria describing the impact and relevance of device differences would not be easily identified. This was because of the diversity of inhaled device designs that exist, the complete product life cycle that was encompassed by the participants, and the lack of an IVIVC for inhaled products. It was, however, possible to reach a broad consensus on a risk-based approach that could be used to assess the potential impact of device differences. This concept would be equally applicable to both innovator and generic devices alike, and could equally be used to evaluate differences that might arise from either intra- or interdevice changes. Examples of the types of device changes that could be assessed include a device and formulation switch (e.g., a generic introduction), a complete switch in device (e.g., during the development of an innovator product), or a device modification (e.g., during product lifecycle management).

The concept of a risk-based approach to assessing device differences is shown schematically in Figure 4.

Logically speaking, as device similarity between the two devices increases, the risk of that device difference impacting product equivalence correspondingly decreases. Any difference in device could therefore be evaluated using a risk assessment approach to assess the likely impact of that difference. The assessment would include consideration of product knowledge, current scientific understanding, and the target product profile of the product and would consider such questions as whether:

- The change is visible to the patient?
- The change impacts the way the patient interacts with the device during the inhalation maneuver (e.g., change in mouthpiece geometry, change in labeling instructions, etc.)?
- The change potentially impacts product performance?

Three examples of possible device differences are described in Figure 4 and are shown from left to right in what might be

considered increasing degree of device similarity. During the discussions, there was considerable debate as to whether this relative order was correct. This debate further underlines the importance of being able to fully define the nature of the device difference on a case by case basis.

Having fully defined the device differences, the risk assessment approach then requires the impact of those differences to be assessed for severity. The paucity of information in the public domain (most likely due to the proprietary nature of the information) and lack of IVIVC to assist in assessment of risk severity makes this part of the assessment difficult. The challenge is therefore to see if there might be a mechanism for establishing a consensus position for assessing the level of risk for device differences.

Having completed the risk assessment, studies might be required to generate data to support the evaluation of the device differences. These studies could be broadly divided into three groups: *in vitro* studies, *in vivo*/human factor studies (which may include clinical studies), and robustness studies.

Much of the discussion on *in vitro* tests related to cascade impaction testing, its relevance, the need to consider ranges of flow rates for DPIs and potential opportunities for improvement such as use of patient profiles with isokinetic sampling. The subject of cascade impaction testing is covered in more detail in Session 1. It was recognized that other types of *in vitro* testing, such as measurement of actuation force, should also be considered to assess device differences.

Human factor tests were those that were considered to test for any impact on the patient interface. These may involve *in vivo* testing such as efficacy and PK/PD studies (see Sessions 2, 3, and 4), but equally would include handling or similar studies. For handling studies, it was noted that, as they depend on the exact nature of the differences between devices, the device being evaluated and the patient population, no standard tests are available, although some guiding principles in this area may be beneficial.

Robustness studies received considerable discussion. Questions raised included whether it is necessary to demonstrate equivalent robustness between devices. If so, what is the relevance of any difference, and is there a minimum acceptable standard that should be met? It was also recognized that differences between devices could lead to different potential misuse scenarios and that would also need to be considered. The question was also raised as to what is an acceptable level for complaints/device failures for two devices to be considered similar, and as such rates are typically low, how could equivalence be demonstrated?

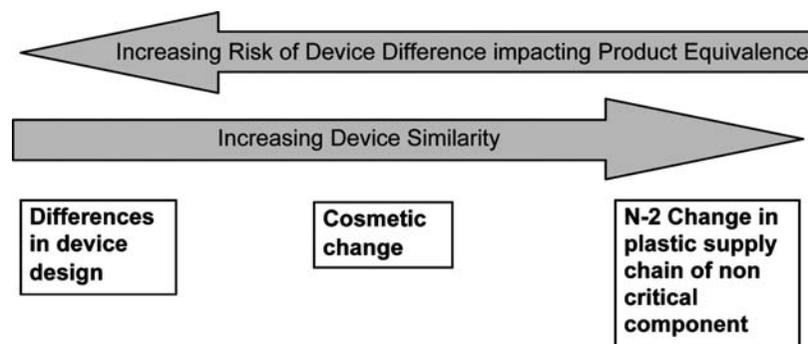


FIG. 4. Schematic representation of a risk-based approach to the assessment of device differences.

Session 5 summary. The level of participation and wide-ranging views expressed by the participants confirmed that the assessment of device similarity is a challenging and complex area throughout the complete product life cycle. When considering if a change or difference in a device design has the potential to impact product BE, it is necessary to consider the change with respect to the formulation being delivered and the way in which the patient uses the device. The diverse nature of inhaled devices means that each situation needs to be considered on a case-by-case basis based on product knowledge, current scientific understanding, and the target product profile of the product. Use of a risk management approach for assessing such differences offers a potential way forward.

Potential future work. The first step in addressing the difficulty of assessing risk severity might be to establish whether there is any form of consensus within the industry at present. This could potentially be through some form of crossindustry/expert survey, which would attempt to classify a number of well-defined device differences.

Workshop Conclusions

This 2-day workshop reviewed the present approaches and made recommendations for demonstrating BE of OIPs for NDAs, ANDAs, and postapproval changes. The outcomes represented a basis for the current scientific understanding and highlighted the areas in which further work is needed. The speakers presented ideas surrounding the applicability and challenges of the “weight of evidence” approach to establishing BE. From that, concepts related to biomarkers such as eNO, dose–response, and PK approaches were offered. The application of criteria and statistical approaches for making decisions related to BE were discussed. In particular, the application of the criteria to specific cases such as products with more than one strength, and combination products was cited as a key area for further examination. *In vitro* methodology for BE (related to pMDIs and DPIs), lung deposition, *in silico* models, and potential links to therapeutic outcomes were also areas that needed more discussion. Agreement on what constitutes device sameness was an area that decidedly required more input. Finally, approaches to establishment of therapeutic equivalence in the EU and utilization of QbD for OIPs were presented.

In-depth discussions from the breakout sessions highlighted that new *in vitro* methods may be needed to establish an IVIVC. There was a clear differentiation between the role of *in vitro* tests for CMC (QC) versus BE applications. However, the statistical interpretation especially between the US and EU of *in vitro* results for BE requires further clarification. There was no clear consensus on the flow rate and simulated inhaled volume for *in vitro* testing of DPIs as it relates to BE.

It was generally agreed that cascade impaction techniques can give a general understanding of lung deposition, but was not well correlated with regional lung deposition. It was concluded that imaging techniques were useful for assessing total and regional lung deposition. However, the application of imaging was considered useful for in-house bridging studies and not seen as a viable option for BE due to issues associated with adulteration from the labeling process. In

addition, standardization of interpretation of regional lung deposition should be addressed.

More input was needed regarding study designs that address duration of action and peak effect for LABAs, patient populations when the drug product can be used in asthmatics and COPD patients, as well as combination products. The concept of dose–response and the ability to discriminate was a topic that circulated through a number of the sessions. The utilization of biomarkers such as eNO showed promise, yet needed validation. Other approaches such as the asthma stability model and PK approaches that address locally acting OIPs also piqued the interest of the audience and represent areas that need additional data.

Clarity around the definition of device sameness as well as the therapeutic relevance of device differences or changes was a key discussion point. Topics such as acceptable differences between instructions for use and labeling between innovator and generic products as well as similarities in device robustness should be debated. Innovations such as the addition of a dose counter on a generic product, or a reduction in the number of actuations to prime a generic pMDI present a challenge to establishing sameness. Material changes, device shape, operating principles, and metering mechanisms also need further definition. The cumulative list of these unanswered questions suggests that at this time there is not a clear pathway for demonstration of bioequivalence of a generic DPI.

Summary of Workshop Action Items

The objective of this conference was to generate recommendations for demonstrating BE for orally inhaled products. The Workshop facilitated both spirited and open discussions. In the end, there were more questions than answers. The outcomes and action items presented below represent the combined efforts of attendees, facilitators, and organizers representing academia, industry, and regulatory bodies on an international scale. A BE road map has been proposed, which will result in future workshops and PQRI Working Groups.

Clinical road map

- PK for OIP with a new workshop, titled Role of Pharmacokinetics in Establishing Bioequivalence for Orally Inhaled Drug Products, scheduled for April 29–30, 2010. The workshop will be held in coordination of RDD 2010 (www.rddonline.org)
- Biomarkers and surrogates for COPD
- Standardization of lung imaging methodology
- Statistical methods for *in vivo* BE

Clinical/CMC road map

- QbD risk analysis relating to changes during development and postapproval
 - Device survey to begin in the third quarter of 2009
 - Formulation changes to begin in the first quarter of 2010

In vitro/in vivo interface road map

- IVIVC Working Group to be established 4Q09
 - Workshop is planned for 2011

Comparative in vitro BE road map

- Statistical methods using CI data for *in vitro* equivalence to begin in the fourth quarter of 2009

Acknowledgments

The workshop would not have been possible without the organization and dedication of Dennis O'Connor, Workshop Chairman, and Vicki Penn, PQRI Executive Secretary.

2009 PQRI Bioequivalence for Locally Acting OIPs Workshop Planning Committee: Dennis O'Connor, B.S., Boehringer Ingelheim Pharmaceuticals, Inc., Chair; Wallace P. Adams, R.Ph., Ph.D., U.S. Food and Drug Administration; Mei-Ling Chen, Ph.D., U.S. Food and Drug Administration; Kevin C. Fitzgerald, R.Ph., GlaxoSmithKline; Svetlana Lyapustina, Ph.D., Drinker, Biddle, and Reath; Paul Lucas, Ph.D., Pfizer; Gary R. Pitcairn, Ph.D., Pfizer; Michael Riebe, Ph.D., Merck&Company, Inc.; Gur Jai Pal Singh, Ph.D., Watson Pharmaceuticals; Julie D. Suman, Ph.D., Next Breath LLC.

2009 PQRI Bioequivalence for Locally Acting OIPs Workshop Speakers, Moderators and Meeting Facilitators: Richard C. Ahrens, M.D., University of Iowa; Mei-Ling Chen, Ph.D., U.S. Food and Drug Administration; Badrul A. Chowdhury, M.D., Ph.D., U.S. Food and Drug Administration; David Christopher, M.S., Schering-Plough; Dale P. Conner, Pharm.D., U.S. Food and Drug Administration; Richard N. Dalby, Ph.D., University of Maryland; Leslie Hendeles, Pharm.D., University of Florida Anthony J. Hickey, Ph.D., University of North Carolina; Günther Hochhaus, Ph.D., University of Florida; Beth L. Laube, Ph.D., Johns Hopkins University School of Medicine; Sau L. Lee, Ph.D., U.S. Food and Drug Administration; Bing V. Li, Ph.D., U.S. Food and Drug Administration; Dennis O'Connor, Boehringer Ingelheim; Neil H. Parikh, B.Pharm., Axar Pharmaceuticals; David A. Parkins, Ph.D., GlaxoSmithKline Prasad Peri, Ph.D., U.S. Food and Drug Administration; Gary R. Pitcairn, Ph.D., Pfizer Michael Riebe, Ph.D., Merck Research Laboratories; Partha Roy, Ph.D., U.S. Food and Drug Administration; Tushar Shah, M.D., Teva Pharmaceuticals; Gur Jai Pal Singh, Ph.D., Watson Pharmaceuticals; Sandra Suarez Sharp, Ph.D., U.S. Food and Drug Administration; Julie D. Suman, Next Breath, LLC; Marjolein Weda, Ph.D., National Institute for Public Health and the Environment, The Netherlands; Janet Woodcock, M.D., U.S. Food and Drug Administration; Lawrence X. Yu, Ph.D., U.S. Food and Drug Administration.

Author Disclosure Statement

PQRI sponsored this event, which included waivers of registration for the authors and travel assistance for academic participants. The following authors have disclosures: D. Parkins is a GlaxoSmithKline shareholder. M. Riebe is a shareholder of Merck & Co. Inc. P. Lucas is a Pfizer shareholder. L. Hendeles has consulted for Advent Pharmaceuticals, Perrigo Company, and MedaPharma. Dr. Hendeles has also received a grant from Sandoz. G. Hochhaus has received research funding or consultantships from Merck, AstraZeneca, GSK, Sandoz, Advent, and Cipla. R. Ahrens has received research funding or serves as a consultant for Abbott Laboratories, Advent Pharmaceuticals, Boehringer Ingelheim, GlaxoSmithKline, Gilead, Inspire Pharmaceuticals, MPEX Pharmaceuticals, Perrigo Pharmaceuticals, PTC

Pharma, Transave Inhalation Biotherapeutics, Vertex Pharmaceuticals, and Watson Pharmaceuticals. The remaining authors indicate no conflict of interest to declare.

List of Abbreviations

Abbreviation	Definition
AAPS	American Association of Pharmaceutical Scientists
ABE	average bioequivalence
ANDA	Abbreviated New Drug Application
API	active pharmaceutical ingredient
APSD	aerodynamic particle size distribution
AUC	area under the curve
BA	bioavailability
BDP	beclomethasone dipropionate
BE	bioequivalence
BID	twice a day
C/P Ratio	central to peripheral
CFC	chlorofluorocarbon
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	cascade impactor; cascade impaction
C _{max}	maximum plasma concentration
CMC	Chemistry, Manufacturing and Controls
COPD	chronic obstructive pulmonary disease
CPP	critical process parameters
DOE	design of experiment
DPI	dry powder inhaler
EMEA	European Medicines Agency
eNO	exhaled nitric oxide
EU	European Union
FEV ₁	forced expired volume in the first second
FP	fluticasone propionate
FPF	fine particle fraction
HFA	hydrofluoroalkane
HV	healthy volunteers
ICS	inhaled corticosteroids
INTFG	Inhalation and Nasal Technology Focus Group
IV/IVC	<i>in vitro</i> - <i>in vivo</i> correlations
LABA	long-acting beta agonist
MVBE	multivariate bioequivalence
NDA	New Drug Application
OGD	Office of Generic Drugs
OIP	orally inhaled product
PAT	process analytical technology
PBE	population bioequivalence
PC20	provocational concentration that reduced FEV ₁ by 20%
PD	pharmacodynamics
PEF	peak expiratory flow
PET	positron emission tomography
PK	pharmacokinetics
pMDI	pressurized metered dose inhaler
PQRI	Product Quality Research Institute
PSD	particle size distribution
QbD	quality by design
QC	quality control
R	reference drug product
RPID	reservoir powder inhalation device
SABA	short-acting beta-agonist

SPECT single photon emission computer
tomography
T test drug product
USP United States Pharmacopeia

References

- U.S. Department of Health and Human Services (DHHS), Food and Drug Administration (FDA): Innovation or Stagnation. March 2004. Available at: <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/ucm113411.pdf>
- DHHS, Center for Drug Evaluation and Research (CDER), FDA, Office of Pharmaceutical Science (OPS), Office of Generic Drugs (OGD): Critical Path Opportunities for Generic Drugs. 1 May 2007. Available at: <http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/ucm077250.htm>
- DeLuca PP, and Lyapustina S: Product quality research institute reports. AAPS PharmSciTech. 2007;8:Article 6.
- Adams WP, Christopher D, Lee DS, Morgan B, Pan Z, Singh GJP, Tsong Y, and Lyapustina S: Product Quality Research Institute evaluation of cascade impactor profiles of pharmaceutical aerosols, Part 1: background for a statistical method. AAPS PharmSciTech. 2007;8:Article 4.
- Christopher D, Adams WP, Lee DS, Morgan B, Pan Z, Singh GJP, Tsong Y, and Lyapustina S: Product Quality Research Institute evaluation of cascade impactor profiles of pharmaceutical aerosols: part 2—evaluation of a method for determining equivalence. AAPS PharmSciTech. 2007;8:Article 5.
- Christopher D, Adams W, Amann A, Bertha C, Byron PR, Doub W, Dunbar C, Hauck W, Lyapustina S, Mitchell J, Morgan B, Nichols S, Pan Z, Singh GJP, Tougas T, Tsong Y, Wolff R, and Wyka B: Product Quality Research Institute evaluation of cascade impactor profiles of pharmaceutical aerosols, Part 3: final report on a statistical procedure for determining equivalence. AAPS PharmSciTech. 2007;8:Article 90.
- Creticos PS, Adams WP, Petty BG, Lewis LD, Singh GJP, Khattignavong AP, Molzon JA, Martinez MN, Lietman PS, and Williams RL: A methacholine challenge dose–response study for development of a pharmacodynamic bioequivalence methodology for albuterol metered-dose inhalers. J Allergy Clin Immunol. 2002;110:713–720.
- Chervinsky P, van As A, Bronsky EA, Dockhorn R, Noonan M, LaForce C, and Pleskow W: Fluticasone propionate aerosol for the treatment of adults with mild to moderate asthma. J Allergy Clin Immunol. 1994;94:676–683.
- Kharitonov SA, Yates D, Robbins RA, Logan-Sinclair R, Shinebourne EA, and Barnes PJ: Increased nitric oxide in exhaled air of asthmatic patients. Lancet. 1994;343:133–135.
- Silkoff PE, McClean P, Spino M, Erlich L, Slutsky AS, and Zamel N: Dose–response relationship and reproducibility of the fall in exhaled nitric oxide after inhaled beclomethasone dipropionate therapy in asthma patients. Chest. 2001;119:1322–1328.
- Currie GP, Bates CE, Lee DKC, Jackson CM, and Lipworth BJ: Effects of fluticasone plus salmeterol versus twice the dose of fluticasone in asthmatic patients. Eur J Clin Pharmacol. 2003;59:11–15.
- Silkoff PE, McClean PA, Slutsky AS, Caramori M, Chapman KR, Gutierrez C, and Zamel N: Exhaled nitric oxide and bronchial reactivity during and after inhaled beclomethasone in mild asthma. J Asthma. 1998;35:473–479.
- Beck-Ripp J, Griese M, Arenz S, Köring C, Pasqualoni B, and Bifulco P: Changes of exhaled nitric oxide during steroid treatment of childhood asthma. Eur Respir J. 2002;19:1015–1019.
- American Thoracic Society: ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. Am J Resp Crit Care Med. 2005;171:912–930.
- Chowdhury BA: *Exhaled Nitric Oxide Model for Inhaled Corticosteroid Dose-Response. Topic 3: Use of Inhaled Corticosteroid Dose Response as a Means to Establish Bioequivalence of Inhalation Drug Products*. FDA/CDER/Advisory Committee for Pharmaceutical Science and Clinical Pharmacology. Rockville, MD, July 23, 2008.
- Adams WP: *Asthma Stability Model For Inhaled Corticosteroid Dose-Response. Topic 3: Use of Inhaled Corticosteroid Dose Response as a Means to Establish Bioequivalence of Inhalation Drug Products*. FDA/CDER/Advisory Committee for Pharmaceutical Science and Clinical Pharmacology. Rockville, MD, July 23, 2008.
- Ahrens RC, Teresi ME, Han S-H, Donnell D, Vanden Burgt JA, and Lux CR: Asthma stability after oral prednisone—a clinical model for comparing inhaled steroid potency. Am J Resp Crit Care Med. 2001;164:1138–1145.
- Crowder TM, Hickey AJ, Louey MD, and Orr N: *A Guide to Pharmaceutical Particulate Science*. Interpharm/CRC Press, Boca Raton, FL, p. 205, 2003.
- WC Hinds: *Aerosol Technology: Properties, Behavior, and Measurement of Airborne Particles*, 2nd ed. Wiley, New York; 1999, chap 11.
- Sbirlea-Apiou G, Caillibotte G, Yang Y, Katz I, and Martonen T: Deposition mechanics of pharmaceutical particles in human airways. In: AJ Hickey (ed). *Inhalation Aerosols: Physical and Biological Basis for Therapy*, Informa Healthcare, New York; 2007, chap 1.
- Olsson B, and Asking L: Critical aspects of the function of inspiratory flow driven inhalers. J Aerosol Med. 1994;7(Suppl 1):S43–S47.
- Newman SP, and Chan H-K: In vitro/in vivo comparisons in pulmonary drug delivery. J Aerosol Med Pulm Drug Deliv. 2008;21:77–84.
- Apiou-Sbirlea G, Simoes-Pichelin M, Caillibotte G, Katz I, Texereau J, Fleming J, Conway J, Scheuch G, and Martonen T: Validated three dimensional CFD modeling of aerosol drug deposition in humans—influence of disease and breathing regimes. In: RN Dalby, PR Byron, J Peart, JD Suman, SJ Farr, and PM Young (eds). *Respiratory Drug Delivery 2008, Book 1*. Davis Healthcare, River Grove, IL; pp. 185–195, 2008.
- Daley-Yates PT, Parkins DA, Thomas MJ, Gillett B, House, KW, and Ortega HG: Pharmacokinetic, pharmacodynamic, efficacy, and safety data from two randomized, double-blind studies in patients with asthma and an in vitro study comparing two dry-powder inhalers delivering a combination of salmeterol 50 µg and fluticasone propionate 250 µg: implications for establishing bioequivalence of inhaled products. Clin Ther. 2009;31:370–385.
- Lin T-C, Breyse PN, Laube BL, and Swift DL: Mouthpiece diameter affects deposition efficiency in cast models of the human oral airways. J Aerosol Med. 2001;14:335–341.
- Fink JB, and Rubin BK: Problems with inhaler use: A call for improved clinician and patient education. Respir Care. 2005;50:1360–1374.
- Molimard M, Raheison C, Lignot S, Depont F, Abouelfath A, and Moore N: Assessment of handling of inhaler devices

- in real life: an observational study in 3811 patients in primary care. *J Aerosol Med.* 2003;16:249–254.
28. Khassawneh BY, Al-Ali MK, Alzoubi KH, Batarseh MZ, Al-Safi SA, Sharara AM, and Alnasr HM: Handling of inhaler devices in actual pulmonary practice: Metered-dose inhaler versus dry powder inhalers. *Respir Care.* 2008;53:324–328.
 29. Melani AS: Inhalatory therapy training: a priority challenge for the physician. *Acta Biomed.* 2007;78:233–245.
 30. European Medicines Agency (EMA): 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 January 2009. Available at: <http://www.emea.europa.eu/pdfs/human/ewp/415100enfin.pdf>
 31. European Medicines Agency (EMA): Points to consider on the requirements for clinical documentation for orally inhaled products (OIP). 22 April 2004.
 32. Health Canada: Guidance to establish equivalence or relative potency of safety and efficacy of a second entry short-acting beta₂-agonist metered dose inhaler. February, 1999. Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/mdi_bad-eng.pdf
 33. Health Canada: Draft guidance. Submission requirements for subsequent market entry inhaled corticosteroid products for use in the treatment of asthma. August, 2007. Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/inhal_corticost-eng.pdf
 34. Chowdhury B: US perspectives on the equivalence of ICS. In: RN Dalby, PR Byron, J Peart, JD Suman, SJ Farr, and PM Young (eds). *Respiratory Drug Delivery 2008, Book 1*. Davis Healthcare International Publishing, River Grove, IL; pp. 148–150, 2008.
 35. Finney DJ: *Statistical Method in Biological Assay*, 3rd ed. Charles Griffin & Co, London; pp. 1–12, 1978.
 36. Becker AB, and Simons FE: Formoterol, a new long-acting selective β₂-agonist, decreases airway responsiveness in children with asthma. *Lung.* 1990;168(Suppl):99–102.
 37. Lipworth B, Tan S, Devlin M, Aiken T, Baker R, and Hendrick D: Effects of treatment with formoterol on bronchoprotection against methacholine. *Am J Med.* 1998;104:431–438.
 38. Ahrens RC, Hendeles L, Clarke WR, Dockhorn RJ, Hill MR, Vaughan LM, Lux C, and Han S-H: Therapeutic equivalence of Spiros dry powder inhaler and Ventolin metered dose inhaler: a bioassay using methacholine. *Am J Respir Crit Care Med.* 1999;160:1238–1243.
 39. Parameswaran KN, Inman MD, Ekholm BP, Morris MM, Summers E, O'Byrne PM, and Hargreave FE: Protection against methacholine bronchoconstriction to assess relative potency of inhaled β₂-agonist. *Am J Respir Crit Care Med.* 1999;160:354–357.
 40. Stewart BA, Ahrens RC, Carrier S, Frosolono M, Lux C, Han S-H, and Milavetz G: Demonstration of in vivo bioequivalence of a generic albuterol metered-dose inhaler to Ventolin. *Chest.* 2000;117:714–721.
 41. Ringdal N, Derom E, Wählin-Boll E, and Pauwels R: Onset and duration of action of single doses of formoterol inhaled via Turbuhaler. *Respir Med.* 1998;92:1017–1021.
 42. Maesen FPV, Costongs R, Smeets SJ, Zweers GMA, and Goedhart DM: Formoterol as dry powder inhalation: a dose finding study in comparison with formoterol metered dose inhaler and placebo. *Chest.* 1992;101:1376–1381.
 43. Palmqvist M, Persson G, Lazer L, Rosenborg J, Larsson P, and Lotvall J: Inhaled dry-powder formoterol and salmeterol in asthmatic patients: onset of action, duration of effect and potency. *Eur Respir J.* 1997;10:2484–2489.
 44. Bousquet J, Huchon G, Leclerc V, Vicaut E, and Lefrançois G: A randomized, double-blind, double-dummy, single-dose, efficacy crossover trial comparing formoterol-HFA (pMDI) versus formoterol-DPI (Aerolizer™) and placebo (pMDI or Aerolizer™) in asthmatic patients. *Respiration.* 2005;72(Suppl 1):6–12.
 45. Pohunek P, Matulka M, Rybníček O, Kopriva F, Honomichlová H, and Svobodová T : Dose-related efficacy and safety of formoterol (Oxis®) Turbuhaler® compared with salmeterol Diskhaler® in children with asthma. *Pediatr Allergy Immunol.* 2004;15:32–39.
 46. Pauwels RA, Löfdahl C-G, Postma DS, Tattersfield AE, O'Byrne P, Barnes PJ, and Ullman A: Effect of inhaled formoterol and budesonide on exacerbations of asthma. *N Engl J Med.* 1997;337:1405–1411.
 47. Busse WW, Brazinsky S, Jacobson K, Stricker W, Schmitt K, Vanden Burgt J, Donnell D, Hannon S, and Colice GL: Efficacy response of inhaled beclomethasone dipropionate in asthma is proportional to dose and is improved by formulation with a new propellant. *J Allergy Clin Immunol.* 1999;104:1215–1222.
 48. Jatakanon A, Kharitonov S, Lim S, and Barnes PJ: Effect of differing doses of inhaled budesonide on markers of airway inflammation in patients with mild asthma. *Thorax.* 1999;54:108–114.
 49. Kelly MM, Leigh R, Jayaram L, Goldsmith CH, Parameswaran K, and Hargreave FE: Eosinophilic bronchitis in asthma: a model for establishing dose–response and relative potency of inhaled corticosteroids. *J Allergy Clin Immunol.* 2006;117:989–994.
 50. Jones SL, Herbison P, Cowan JO, Flannery EM, Hancox RJ, McLachlan CR, and Taylor DR: Exhaled NO and assessment of anti-inflammatory effects of inhaled steroid: dose–response relationship. *Eur Respir J.* 2002;20:601–608.
 51. Kharitonov SA, Donnelly LE, Montuschi P, Corradi M, Collins JV, and Barnes PJ: Dose-dependent onset and cessation of action of inhaled budesonide on exhaled nitric oxide and symptoms in mild asthma. *Thorax.* 2002;57:889–896.
 52. Woodcock J: The concept of pharmaceutical quality. *Am Pharm Rev.* 2004;7:10–15.
 53. DHHS, FDA, CDER, Center for Biologics Evaluation and Research (CBER): June 2009. Guidance for Industry: Q8(R1) Pharmaceutical Development. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073507.pdf>
 54. Yu LX: Pharmaceutical quality by design: product and process development, understanding, and control. *Pharm Res.* 2008;25:781–791.
 55. DHHS, FDA, CDER: October 1998. Draft Guidance for Industry: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products: Chemistry, Manufacturing, and Controls Documentation. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070573.pdf>
 56. DHHS, FDA, CDER: April 2003. Draft Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070111.pdf>

57. DHHS, FDA, CDER: 11 April 2003. Statistical Information from the June 1999 Draft Guidance and Statistical Information for In Vitro Bioequivalence Data Posted on August 18, 1999. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070118.pdf>
58. Advair Diskus labeling: April 2008, GlaxoSmithKline, Research Triangle Park, NC. Available at: <http://www.advair.com/index.html>
59. <601>: Aerosols, nasal sprays, metered-dose inhalers, and dry powder inhalers *U.S. Pharmacopeia 32/National Formulary 27*, United States Pharmacopeial Convention, Rockville, MD, 2009.
60. Chavan V, and Dalby R: Effect of rate of rise in simulated inspiratory air flow on dry powder inhaler (DPI) performance. In: RN Dalby, PR Byron, SJ Farr, and J Peart (eds). *Respiratory Drug Delivery VII*, Vol II. Serentec Press, Raleigh, NC; pp. 593–596, 2000.
61. Bagger-Jorgensen H, Sandell D, Lundback H, and Sundahl M: Effect of inherent variability of inhalation products on impactor mass balance limits. *J Aerosol Med.* 2005;18:367–378.
62. O'Connor D, Tougas T, Patel R, Davidson W, and Carr D: The discriminatory nature of the spray pattern test. *AAPS J* 2005;7(Suppl 2):Abstract 668.
63. DHHS, FDA, CDER: July 2002. Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products—Chemistry, Manufacturing, and Controls Documentation. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070575.pdf>
64. Guo C, Ye W, Kauffman J, and Doub WH: Evaluation of impaction force of nasal sprays and metered-dose inhalers using the texture analyser. *J Pharm Sci.* 2008;98:2799–2806.
65. DHHS, FDA, CDER: *Approved Drug Products with Therapeutic Equivalence Evaluations ("Orange Book")*, 29th ed, 2009, Section 1.2. Therapeutic equivalence-related terms, pp. vi–viii. Available at: <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf>
66. Biomarkers Definitions Working Group: Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. *Clin Pharmacol Ther.* 2001;69:89–95.
67. DHHS, FDA, CDER: 2 June 1995, Guidance: Topical Dermatologic Corticosteroids: In Vivo Bioequivalence. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070234.pdf>
68. Cockcroft DW, Killian DN, Mellon JJA, and Hargreave FE: Bronchial reactivity to inhaled histamine: a method and clinical survey. *Clin Allergy.* 1977;7:235–243.
69. Geoffroy P, Lalonde RL, Ahrens R, Clarke W, Hill MR, Vaughan LM, and Grossman J: Clinical comparability of albuterol delivered by the breath-actuated inhaler (Spiros®) and albuterol by MDI in patients with asthma. *Ann Allergy Asthma Immunol.* 1999;82:377–382.
70. Derom EY, Pauwels RA, and Van Der Straeten MEF: the effect of inhaled salmeterol on methacholine responsiveness in subjects with asthma up to 12 hours. *J Allergy Clin Immunol.* 1992;89:811–815.
71. Ahrens RC, Teresi ME, Han S-H, Donnell D, Vanden Burgt JA, and Lux CR: Asthma stability after oral prednisone: a clinical model for comparing inhaled steroid potency. *Am J Respir Crit Care Med.* 2001;164:1138–1145.
72. Ahrens RC, Hendeles L, Teresi ME, Lux CR, Vanden Burgt J, Hart KA, and Ekholm BP: Stability of asthma following maximization of lung function with a high-dose inhaled corticosteroid (ICS) burst: a more precise method for comparing clinical potency of ICS. *J Aerosol Med.* 2003; 16:197.
73. Fuglsang A, Leach C, and Mayers I: Therapeutic equivalence of inhaled corticosteroids—workshop on regional differences in regulatory requirements. In: RN Dalby, PR Byron, J Peart, JD Suman, SJ Farr, and PM Young (eds). *Respiratory Drug Delivery 2008, Book 1.* Davis Healthcare, River Grove, IL; pp. 133–147, 2008.
74. Lipworth BJ, Sims EJ, Das SK, Buck H, and Paterson M: Dose–response comparison of budesonide dry powder inhalers using adenosine monophosphate bronchial challenge. *Ann Allergy Asthma Immunol.* 2005;94:675–681.
75. Ahrens RC: Proving inhaled corticosteroid equivalence: what are the clinically acceptable differences in performance? In: RN Dalby, PR Byron, J Peart, JD Suman, SJ Farr, and PM Young (eds). *Respiratory Drug Delivery 2008, Book 1.* Davis Healthcare, River Grove, IL, 2008, pp. 101–108.
76. Newman SP, and Pitcairn GR: Gamma scintigraphy and SPECT. In: G Lappin G, and S Temple, (eds). *Radiotracers in Drug Development.* CRC Press, Boca Raton, FL; chap 12, 2006.
77. Newman SP, Pitcairn GR, Hirst PH, and Rankin L: Radionuclide imaging technologies and their use in evaluating asthma drug deposition in the lungs. *Adv Drug Deliv Rev.* 2003;55:851–867.
78. Newman SP, Hirst PH, Pitcairn GR, and Clark AR: Understanding regional lung deposition data in gamma scintigraphy. In: RN Dalby, PR Byron, and SJ Farr SJ, (eds). *Respiratory Drug Delivery VI.* Interpharm Press, Buffalo Grove, IL; pp. 9–15, 1998.
79. Pitcairn GR, and Newman SP: Radiolabelling of dry powder formulations. In: RN Dalby, PR Byron, and SJ Farr, (eds). *Respiratory Drug Delivery VI.* Interpharm Press, Buffalo Grove, IL; pp. 397–399, 1998.
80. Snell NJC, and Ganderton D: Assessing lung deposition of inhaled medications. *Respir Med.* 1999;93:123–133.
81. Singh GJP, and Adams WP: US regulatory and scientific considerations for approval of generic locally acting orally inhaled and nasal drug products. In: RN Dalby, PR Byron, J Peart, and JD Suman, (eds). *Respiratory Drug Delivery Europe 2005.* Davis Healthcare, River Grove, IL; pp. 115–125, 2005.
82. Chowdhury BA: The regulatory demands of clinical testing protocols for powder inhalers in the USA. In: RN Dalby, PR Byron, J Peart, and JD Suman (eds). *Respiratory Drug Delivery Europe 2007.* Davis Healthcare, River Grove, IL; pp. 101–107, 2007.
83. Hochhaus G: Bioequivalence of inhaled corticosteroids-with emphasis on pharmacokinetic tools. In: *PQRI Workshop on Demonstrating Bioequivalence of Locally Acting Orally Inhaled Drug Products.* Bethesda, MD, March 9–10, 2009. Available at: http://www.pqri.org/workshops/Bioequiv/imagespdfs/final/Hochhaus_final.pdf
84. Borgström L, and Nilsson M: A method for determination of the absolute pulmonary availability of inhaled drugs: Terbutaline. *Pharm. Res.* 1990;7:1068–1070.
85. Thorsson L, Edsbäcker S, and Conradson T-B: Lung deposition of budesonide from Turbuhaler is twice that from a pressurized metered-dose inhaler P-MDI. *Eur Respir J.* 1994; 7:1839–1844.

WORKSHOP SUMMARY REPORT: BIOEQUIVALENCE OF OIPs

29

86. Thorsson L, and Edsbacker S: Lung deposition of budesonide from a pressurized metered-dose inhaler attached to a spacer. *Eur Respir J*.1998;12:1340–1345.
87. Bennett JA, Harrison TW, and Tattersfield AE: The contribution of the swallowed fraction of an inhaled dose of salmeterol to its systemic effects. *Eur Respir J*. 1999;13:445–448.
88. Ward JK, Dow J, Dallow N, Eynott P, Milleri S, Ventresca GP. Enantiomeric disposition of inhaled, intravenous and oral racemic-salbutamol in man—no evidence of enantioselective lung metabolism. *Br J Clin Pharmacol* 2000;49:15–22.
89. Silkstone VL, Corlett SA, and Chrystyn H: Determination of the relative bioavailability of salbutamol to the lungs and systemic circulation following nebulization. *Br J Clin Pharmacol*. 2002;54:115–119.
90. Singh G. Agenda Item: Bioequivalence of Albuterol MDIs. Joint Meeting of the Advisory Committee for Pharmaceutical Science and the Pulmonary-Allergy Drugs Advisory Committee. FDA, Gaithersburg, MD. 16 August 1996, Transcript, pp. 53–68.
91. Chowdhury BA: The FDA critical path initiative: clinical considerations for demonstration of dose–response for inhaled corticosteroids—exhaled nitric oxide model. In: *PQRI Workshop on Demonstrating Bioequivalence of Locally Acting Orally Inhaled Drug Products*, Bethesda, MD, March 9–10, 2009. Available at: http://www.pqri.org/workshops/Bioequiv/imagespdfs/final/Chowdhury_9Mar09_PQRI.pdf
92. Joint Statement of the American Thoracic Society and the European Respiratory Society: ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide. 2005. *Am J Respir Crit Care Med*. 2005;171:912–930.
93. Silkoff PE, Carlson M, Bourke T, Katial R, Ogren E, and Szeffler SJ: The aerocrine exhaled nitric oxide monitoring system NIOX is cleared by the US Food and Drug Administration for monitoring therapy in asthma. *J Allergy Clin Immunol*. 2004;114:1241–1256.
94. Tarsin W, Assi KH, and Chrystyn H: In-vitro intra- and inter-inhaler flow rate-dependent dosage emission from a combination of budesonide and eformoterol in a dry powder inhaler. *J Aerosol Med*. 2004;17:25–32.
95. Richards R, Simpson SF, Renwick AG, and Holgate ST: Inhalation rate of sodium cromoglycate determines plasma pharmacokinetics and protection against AMP-induced bronchoconstriction in asthma. *Eur Respir J*. 1988;1:896–901.
96. Pedersen S, Hansen OR, and Fuglsang G: Influence of inspiratory flow rate upon the effect of a Turbuhaler. *Arch Dis Child*. 1990;65:308–310.
97. Engel T, Scharling B, Skovsted B, and Heinig JH: Effects, side effects and plasma concentrations of turbutaline in adult asthmatics after inhaling from a dry powder inhaler device at different inhalation flows and volumes. *Br J Clin Pharmacol*. 1992;33:439–444.

Received November 1, 2009
in final form, November 2, 2009

Address correspondence to:
Julie D. Suman
Next Breath, LLC
1450 South Rolling Road
Baltimore, MD 21227

E-mail: julie.suman@nextbreath.net

