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Meeting Report

Theme: Current Scientific and Regulatory Approaches for Development of Orally Inhaled and Nasal Drug Products
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Pharmacokinetics of Orally Inhaled Drug Products

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Abstract. The presentations at the Orlando Inhalation Conference on pharmacokinetic (PK) studies indicated that PK is the most sensitive methodology for detecting formulation differences of oral inhaled drug products (OIDPs) that have negligible gastrointestinal bioavailability or for which oral absorption can be prevented (e.g., ingestion of charcoal). PK studies, therefore, may represent the most appropriate methodology for assessing local and systemic bioequivalence (BE). It was believed by many (but not all participants) that potential differences between formulations are more likely to be detected in healthy adult volunteers, as variability is reduced while deposition to peripheral areas is not restricted. A study design allowing assessment and statistical consideration of intra-subject and inter-batch variability within the evaluation of BE studies was suggested, while optimal inhalation technique during PK studies should be enforced to decrease variability. Depending on the drug and *in vitro* method, *in vitro* tests may not detect differences in PK parameters. Harmonization of BE testing requirements among different countries should be encouraged to improve global availability of low cost OIDPs and decrease industry burden.

INTRODUCTION

This paper is part of a series of reports from the "Orlando Inhalation Conference-Approaches in International Regulation" co-organized by the University of Florida and the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) held in March 2014.

Demonstration of BE for oral dosage forms intended to deliver the drug after gastrointestinal absorption *via* the bloodstream is generally based on the statistical comparison of relevant pharmacokinetic (PK) parameters between the test (T) and reference (R) drug products. The reason for pharmacokinetic (PK) studies playing such a central role in BE regulatory decision-making is that potential differences in R and T blood/serum/plasma drug concentration profiles [peak concentration (C_{max}) and area under the concentration-time curve (AUC)] are indicative of significant differences "in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action" (1) as blood is upstream of the site of drug action. In addition, the linear relationship between the delivered dose and relevant PK parameters, such as AUC and C_{max}, makes PK more sensitive than pharmacodynamics/clinical studies that show a non-linear relationship between exposure and effect.

For OIDPs (metered dose and dry powder inhalers), U.S. Food and Drug Administration's (FDA) current practice is that traditional PK studies, evaluating time profiles of blood/plasma/serum drug concentrations, are downstream of the site of action and, therefore, cannot evaluate bioequivalence at the site of drug action.

Discussions among representatives of industry, regulatory agencies, and academia about extending the role of pharmacokinetics for making BE decision of orally inhaled drug products first took place at the 2009 Product Quality Research Institute (PQRI) workshop demonstrating bioequivalence of locally acting orally inhaled drug products (2). The strong interest in extending the role of PK within BE decisions for OIDPs resulted in a second workshop in 2010 organized by PQRI and Respiratory Drug Delivery (RDD) solely discussing the role of PK (3). The Orlando Inhalation Conference continued these discussions on the role of PK as the sole basis for demonstration of BE for OIDPs in a number of presentations and a round table discussions.

PK AND OIDPS

The presentations by Drs. Rebello (4) and Lionberger (5) provided state-of-the-art information on the design of PK studies and what information one can extract from them.

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Following administration of OIDPs, only a small fraction (10–60% of the delivered dose) is deposited in the airways (Fig. 1). As the rest is swallowed, this fraction can be absorbed into the bloodstream from the GI tract if the drug is orally bioavailable. Under these conditions, blood concentrations are determined by the extent and rate with which the drug is absorbed from the lung and the GI tract. Pharmacokinetic studies performed under such a scenario will not allow making conclusions on the pulmonary fate of the OIDP, but provide information on the overall systemic spill-over to assess the safety (Table I). This information is currently necessary for Agência Nacional de Vigilância Sanitária (ANVISA), FDA, and European Medicines Agency (EMA).

Oral bioavailabilities of OIDPs can range from almost zero (mometasone furoate, fluticasone propionate) to up to 50% for salbutamol (6). If distinct differences in the rate of absorption exist between the two pathways, PK studies are able to differentiate between them by determining partial AUCs (Table I). As an example, monitoring salbutamol in the urine over the first 30 min post-inhalation has been shown to be a good indicator for how much salbutamol entered the systemic circulation through pulmonary absorption (7).

In order to assess the pulmonary fate of OIDPs, absorption from the GI tract needs to be negligible (Table I), such as for fluticasone propionate or mometasone furoate or blocked through co-administration of charcoal (8). Under such conditions, PK studies will be able to assess relevant pulmonary deposition characteristics (Tables I and II), such as the available pulmonary dose. This parameter differs from the pulmonary deposited dose as for drugs that dissolve slowly, a significant portion of the deposited drug will be removed from the upper parts of the lung through the mucociliary clearance (9), swallowed, and therefore not available for inducing pulmonary effects. It has been proposed that for slowly dissolving drugs, the mucociliary clearance mechanism might be the basis for discerning between *R* and *T* products with different central to peripheral deposition ratio (10) which in turn will determine potential differences in the dose remaining in the lung *versus* drug entering the bloodstream. As a consequence, AUCs should be larger for formulations that deposit more peripherally (Fig. 2). Thus, PK studies should be able to answer three key questions concerning pulmonary bioequivalence: (1) Is the dose available to the lung equivalent? (2) Do the deposited drugs stay in the airways for an equivalent time? and (3) Is the geography of deposition equivalent (central *vs* peripheral; *c*/*p* ratio)?

Within the discussions at the conference, the majority of participants seem to agree that PK studies can detect potential differences in the available dose and the pulmonary residence time between *R* and *T* products with much higher resolution than possible through clinical studies. However, future research studies need to clarify whether PK is also superior to pharmacodynamic (PD) studies in providing information about the regional deposition of a drug following inhalation. This parameter affected by formulation-dependent factors, inspiratory flow, and airway caliber has affected the outcome or pharmacodynamic studies for selected APIs by affecting the degree of the bronchoconstriction induced by histamine (11, 12). Studies sponsored by FDA are currently underway to answer this question (*vide infra*).

SUBJECT POPULATION/STUDY DESIGN

Deposition of inhaled drugs is affected by several factors including patient factors, such as lung function (4). Systemic availability of slowly dissolving drugs such as fluticasone propionate decrease with decreased lung function, as more drug is delivered centrally (9). FDA recommends PK studies be performed in healthy volunteers. EMA originally suggested that these studies be conducted in patients (13), but

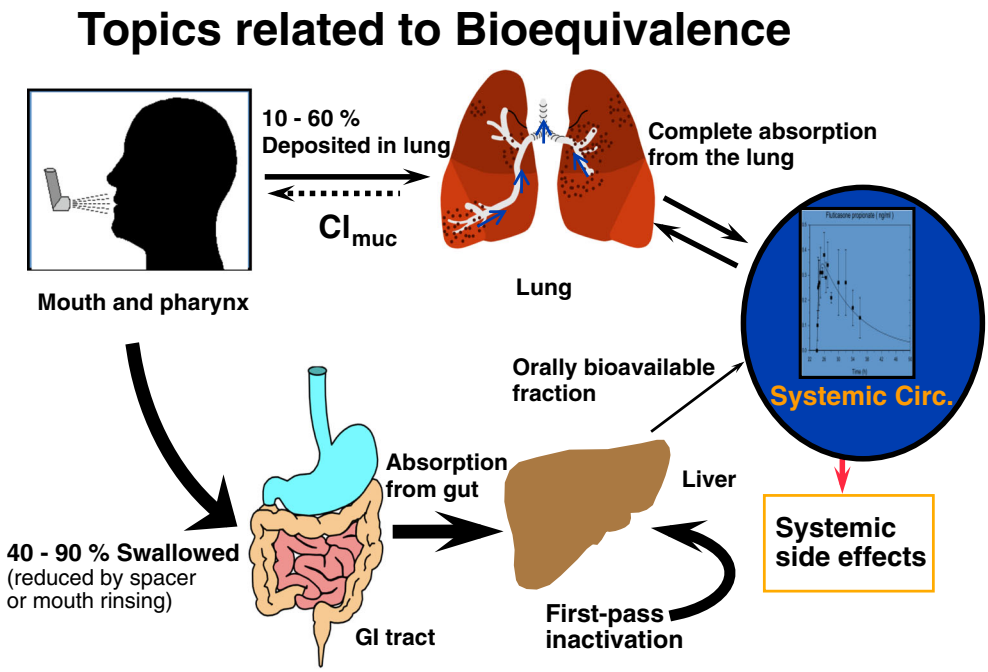

Fig. 1. Scheme describing the fate of inhalation drugs

Table I. PK Study Designs, Active Pharmaceutical Ingredient API Properties, and Ability to Judge Safety and Efficacy Parameters

Oral bioavailability (F) of API	PK parameters	Relevance for safety and efficacy
API with $F>0$	Full PK profile (AUC, C_{max})	Safety (rate and extent)
API with $F>0$	Partial AUC	Efficacy (rate and extent)
$K_{a,pulm} \neq k_{a,oral}$		
API with $F=0$	Full PK profile (AUC, C_{max})	Efficacy, safety (rate and extent)
		c/p ratio for small k_a (?????)
API with $F>0$, charcoal	Full PK profile (AUC, C_{max})	Efficacy
		c/p ratio for small k_a (?????)

currently also accepts PK studies in healthy volunteers to reduce variability.

It was also strongly suggested that subjects need to be trained using suitable devices for DPI or MDI application (4) or measure the actual inhalation flow during drug delivery (14), as differences in inhalation rate will significantly affect lung deposition.

REGULATORY VIEWS ON PK STUDIES

Presentations from Dr. Lionberger (FDA (5)), Dr. Alfredo Garcia-Arieta (EMA (15)), and Gustavo Mendes Lima Santos (ANVISA (16)) highlighted the current differences between regulatory agencies with respect to PK studies (Fig. 3).

Within Guidance for Industry, e.g., the recent guidance on albuterol (17) and fluticasone/salmeterol (18), FDA limits the PK studies to the interpretation of differences in the systemic exposure of OIDPs, although research is underway to evaluate PK studies for assessing the pulmonary equivalence of *R* and *T* products. This approach differs from the approaches ANVISA and EMA are taking.

ANVISA's current thinking was presented by Mr. Gustavo Mendes Lima Santos (16). While the related guidance has not yet been published, ANVISA considers a combination of *in vitro* tests (including cascade impactor studies and determination of the dissolution rates in physiologically relevant dissolution medium) in combination with PK studies (with and without charcoal, if necessary) to demonstrate pulmonary BE using standard BE metrics (90% CI within 0.8 to 1.25). If the drug shows significant oral bioavailability, a second PK study without blocking the GI absorption has to be performed to assess safety using the same BE metrics. PD/clinical studies are only recommended when PK studies cannot be performed (e.g., lack of sufficient analytical sensitivity).

EMA's position as described by Dr. Alfredo Garcia-Arieta (15) has not changed recently, and pharmacokinetics (with charcoal, if necessary) is being used in EMA's stepwise approach ((1) *In vitro*, (2) PK, (3) clinical studies) as second step for demonstrating equivalence in efficacy and safety. Within this stepwise approach, EMA allows PK studies now in healthy volunteers for final bioequivalence decisions even if *in vitro* tests do not show equivalence.

The recommended study design depends on drug specific features of the active pharmaceutical ingredient (API). When oral bioavailability is zero or prevented through charcoal co-treatment, the difference in the AUCs are indicative of differences in the dose reaching the airways, while C_{max} might be sensitive to differences in the regional deposition pattern. For drugs with no absorption from the GI tract [ipratropium, tiotropium, nedocromil, or with almost complete first pass effect (fluticasone propionate, ciclesonide)], one PK study is sufficient for assessing safety and efficacy. For drugs with significant but delayed absorption from the GI tract and very quick lung absorption (salbutamol, salmeterol), partial AUCs (e.g., $AUC_{0-30\ min}$) might be used for efficacy assessment. EMA suggests conducting two PK studies for drugs with significant GI absorption, whose oral and pulmonary absorption cannot be de-convoluted. One study is performed in the absence of charcoal to assess the safety, while a second PK study is performed in the presence of activated charcoal to assess potential differences in pulmonary delivery.

In contrast to ANVISA and FDA, EMA recommends the conduct of the BE study with and without the use of spacers and studies in the pediatric population. This is a challenge in some countries because of the lack of centers with required expertise in performing studies in children and the need for a large sample size due to distinct variability within this population (limitations in optimizing the inhalation procedure through training, variability associated with breathing pattern (4), and countries that do not allow pharmacokinetic studies in the pediatric population because of ethical reasons).

EMA, FDA, and industry discussed challenges associated with the batch-to-batch variability of the reference product and their effect on the outcome of PK BE studies. This variability will especially represent a challenge if only a limited number of batches are available.

Table II. Comparison of *In Vitro*, PK and Pharmacodynamic Studies to Evaluate Relevant Airway-Related Parameters for BE Assessments

	In vitro/scintigraphy	PK	Clinical
Dose delivered to airways	+	−	−
Pulmonary available dose	−	+	± dependent on slope of dose-response
Pulmonary residence time	−	+	No data
Central/peripheral ratio	Likely, studies needed	Likely, studies needed	Limited data for commercial products, studies needed

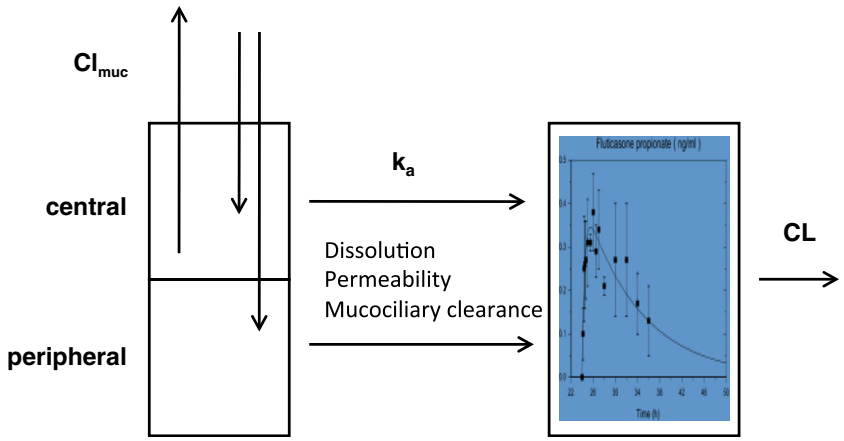

Fig. 2. Effect of dissolution rate, geography of deposition, and mucociliary clearance on systemic exposure (assuming negligible oral bioavailability). Cl_{muc} mucociliary clearance, k_a absorption rate constant, CL systemic clearance

Dr. Lionberger (5) stressed that the goal of PK studies should be to demonstrate that the mean of reference and test products across all batches and the life cycle of the product are equivalent. Challenges within the PK BE study design are the potentially high intra-subject and pronounced R inter-batch variabilities. While the "lucky batch approach (keep doing studies until one batch passes)" has been entertained in the past by the FDA, Dr. Lionberger stressed that FDA is open to alternative PK study designs. He recommended discussing such alternative approaches with the FDA within

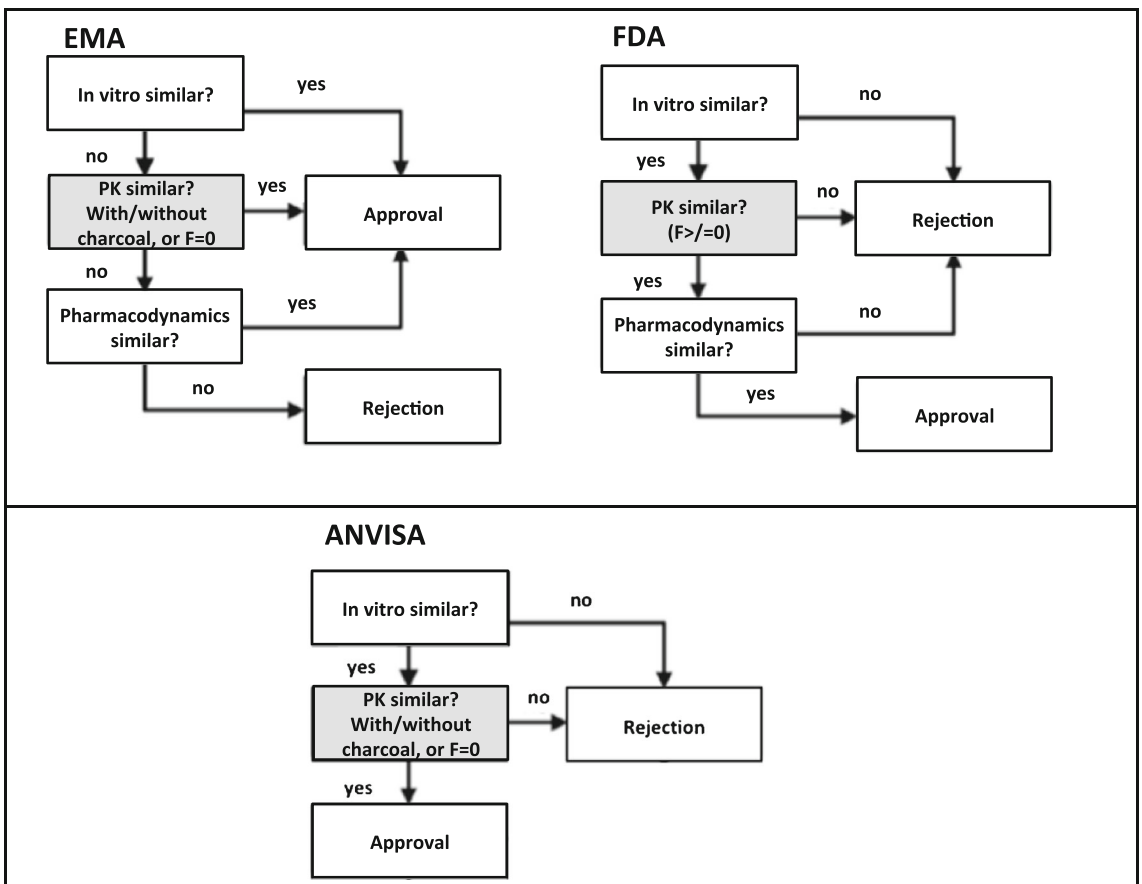

Fig. 3. Comparison of pharmacokinetics, pharmacodynamics studies, and scintigraphy for BE decisions

a requested pre-ANDA meeting. Such meetings are granted for high impact issues (no generic available, product with unique regulatory science issues, or presentation of pilot studies of alternative approaches). FDA encourages pilot study designs that would allow for a clear differentiation between inter-batch and intra-subject variability before proposing a novel pivotal bioequivalence study design. Dr. Lionberger stressed in his presentation that PK studies comparing two batches of the reference with one other batch of the test product will not be suitable to assess batch-to-batch nor intra-subject variability, as such a design does not allow differentiation between the two factors. A study incorporating a repeat of the same *R* batch together with the *T* batch would allow quantification of the intra-subject variability and application of statistical tools for highly variable drugs (19, 20) but would not capture batch-to-batch variability. To include batch-to-batch and intra-subject variability of the reference product, the comparison of one batch of the test product with two batches of the *R* product, with one *R* batch being repeated, was suggested. For showing BE of a *T* product, a randomized, four-way cross-over design would then be necessary.

OTHER PK-RELATED CHALLENGES

An additional problem is sometimes associated with the unavailability of reference products in the country of interest (4). Often, the established ranges of *in vitro* specifications of the innovator product are wide (>20%) especially for DPIs. In addition, because of aging during storage, aerodynamic performance parameters might further change. Industry participants felt that this makes it difficult for some batches of the *R* product to be equivalent against another batch of the *R* product. The choice of the *R* batch might affect the outcome of the PK BE study. Further studies to evaluate batch-to-batch variability would be important to be performed. In addition, the procedure for batch selection should be harmonized between regulatory agencies. EMA suggests the use of representative batches based on cascade impactor studies while, currently, FDA does not specify the batches to be used for PK studies.

While the current FDA draft guidances recommend clinical studies with PD endpoints for assessing pulmonary BE (e.g., efficacy) for OIDPs, guidances for industry for assessing BE of other topical formulations [e.g., lidocaine patches (21) and mesalamine oral dosage form (22)] assesses local BE through PK studies without the need of clinical/PD studies. However, FDA is currently evaluating whether similar approaches might be feasible for slowly dissolving OIDPs, as AUC and C_{max} estimates are likely to be sensitive not only to differences in the available (deposited) dose and potential differences in the dissolution rate, but also to differences in the central to peripheral deposition ratio.

From an industry perspective (4), it was stressed that the most sensitive methodology should be employed for PK BE assessment, with a population most able to demonstrate differences (e.g., healthy volunteers). Because of the distinct differences between regulatory approaches, harmonization of BE guidances for OIDPs across countries would improve global availability. Further, improved communication between industry and regulators would be necessary to build best practices (subject population, appropriate study design, necessity to perform studies in children, selection of *R* batches, *etc.*).

IN VITRO -PK CORRELATIONS

Evaluation of OIDPs is based heavily on *in vitro* studies (such as aerodynamic particle size distribution, spray pattern for MDIs, *etc.*). While a significant effort focuses on the evaluation of OIDPs through *in vitro* tests, the validation of these *in vitro* tests through proper *in vitro in vivo* (IVIVC) correlations is just in its infancy. Interestingly, when multiple dosing strengths of an inhalation product are assessed, EMA does not insist on PK studies for all dosing strengths. If pharmacokinetic BE is demonstrated for the higher dose, it is sufficient for the lower dose formulation to agree in the fine particle dose with the *R* product. This differs from FDA's thinking, as PK studies on all strength are recommended. Numerous presentations stressed the lack of IVIVC for this parameter if performed with standard methodology without the use of conditions that mimic the patients breathing pattern and more realistic throat (*vide infra*). FDA (5) in contrast will only allow *in vitro* data as substitute for PK studies, if PK has shown to be predictable from *in vitro* data. Although FDA has been generally skeptical of model-based BE (with bias to non-compartmental methods), FDA might be willing to accept *in vitro* data as surrogate for *in vivo* BE studies if the applicant has established an IVIVC for *T* and *R* products.

During the conference, several presenters reviewed studies correlating *in vitro* parameters [mainly delivered dose (DD) and fine particle dose (FPD) to PK outcomes]. A good relationship was reported by Reisner (23), as similar delivered doses and FPD were reflected in comparable PK properties of the tested MDI and DPI formulations of formoterol.

Horhota (24) (presented as a stand-alone paper elsewhere in this issue) provided an interesting case study on the *in vitro* [Anderson cascade impactor (ACI)], PK and PD evaluation of tiotropium/salmeterol combination in COPD patients using three different DPI systems high resistance (HandiHaler® containing tiotripium), low resistance device (Diskus®) containing salmeterol and high resistance salmeterol/tiotropium combination device (HandiHaler-2®).

While the impactor-sized mass was equivalent for the tiotropium in single (Spiriva) and combination (tiotropium and salmeterol) HandiHaler® devices, the PK behavior differed significantly, as the combination showed a very fast absorption for tiotropium with a slightly higher systemic exposure (AUC) compared to the tiotropium reference product. ACI tests suggested similar (within 15%) fine particle doses also for salmeterol when given alone or in combination; however, the HandiHaler 2® combination provided a much faster absorption for salmeterol while the systemic exposure was much smaller with the HandiHaler 2® combination product. Interestingly, the effect on lung function in COPD patients was similar between the combination product and the combined use of the mono products. This is not surprising since the dose-response of bronchodilators in COPD is flat. The discrepancies between *in vitro* and PK studies suggest that PK studies are more sensitive to

differences in the DPI formulations than ACI studies. The following might be possible explanations. One reason could be that a potential *in vitro* performance difference was not captured in the ACI studies as more optimized techniques (e.g., Alberta throat with simulated breathing pattern) were not employed. Alternatively, differences between *T* and *R* product, not captured by *in vitro* deposition studies, might be responsible for differences in the PK behavior (e.g., dissolution rate differences due to differences in crystal structure, *etc.*). Overall, further studies need to be performed on establishing IV/IV correlations, not only for the deposited dose but also potentially for regional and post-deposition events.

CONCLUSION

There were numerous examples discussed during the meeting where *in vitro* tests were not predictive of the outcome of PK studies. Improvements have been made in optimizing the methodology employed for the aerodynamic size distribution by using more appropriate throat geometries and natural breathing cycles with some success to predict the pulmonary delivered dose. However, the relationship between regional pulmonary deposition and cascade impactor stage profiles as well as its relationship to PK is currently poorly understood. In addition, not all drug properties relevant for the pulmonary fate of OIDPs are captured by the currently used cascade impactor techniques as such events are downstream of particle deposition (e.g., dissolution rate) or involve post-deposition physiological phenomena (mucociliary clearance). As current *in vitro* approaches do not consider such processes, there is likely to be a discrepancy between *in vitro* and PK studies for slowly dissolving drugs, since the PK behavior is determined significantly by mucociliary clearance. Scintigraphy studies while able to detect differences in the *c*/*p* ratio are not able to detect differences in the pulmonary available dose (Table II). Pharmacokinetic studies should therefore be used as an integral part for evaluating the pulmonary equivalence of OIDPs, especially as pharmacodynamic studies often lack sensitivity.

Conflict of Interest Dr. Hochhaus is the PI on research grants to the University of Florida for the FDA, Astra-Zeneca, and Compleware. Dr. Horhota is an employee of Boehringer-Ingelheim. Dr. Hendeles is the PI on research grants to the University of Florida for GlaxoSmithKline, Teva, and Novartis. Dr. Suarez has no conflicts. Dr. Rebello is an employee of Cipla.

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