
Meeting Report

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

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Current Scientific and Regulatory Approaches for Development of Orally Inhaled and Nasal Drug Products: Overview of the IPAC-RS/University of Florida Orlando Inhalation Conference

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Abstract. This article summarizes discussions at the March 2014 conference organized by the University of Florida (UF) and International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS), entitled “Orlando Inhalation Conference: Approaches in International Regulation.” The special focus of the conference was on global scientific and regulatory issues associated with the testing and demonstration of equivalence for the registration of orally inhaled drug products (OIDPs) in the United States, Europe, Brazil, China, and India. The scope included all types of OIDPs throughout their lifecycle, e.g., innovator/brand-name products, generics, modifications due to lifecycle management, device changes, etc. Details were presented for the U.S. “weight of evidence approach” for registration of generic products (which includes demonstration of *in vitro* and *in vivo* equivalence, as well as quantitative and qualitative sameness, and device similarity). The European “stepwise” approach was elucidated, and the thinking of regulatory agencies in the major emerging markets was clarified. The conference also highlighted a number of areas that would benefit from further research and discussion, especially around patient/device interface and human factor studies, statistical methods and criteria for demonstrating equivalence, the relative roles of *in vivo* and *in vitro* tests, and appropriate designs and metrics for *in vivo* studies of inhaled drugs.

KEY WORDS: bioequivalence; emerging markets; generics; MDIs and DPIs; regulatory science.

INTRODUCTION

OIDPs are a staple of medical treatment for patients with respiratory conditions. Yet because most of these drugs are designed to act locally in the respiratory tract and because the dose delivered to the patient depends on the patient’s inhalation technique, disease state and as well as device characteristics, the suite of tests, and requirements for demonstrating safety and effectiveness of OIDPs is still an

evolving area of regulatory science, especially for generic drug products that have to demonstrate equivalence to the innovator product. Another layer of complexity is added by the international diversity of medical and regulatory approaches towards the testing and registration of both new and generic OIDPs. The purpose of the 2014 IPAC-RS/UF conference, therefore, was to provide a public forum for discussion of the latest research and regulatory thinking regarding registration of OIDPs such as metered dose

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ABBREVIATIONS: BE, bioequivalence; DPI, dry powder inhaler; EU, European Union; FDA, Food and Drug Administration (of the United States); IPAC-RS, International Pharmaceutical Aerosol Consortium on Regulation and Science; MDI, metered dose inhaler; OIDP, orally inhaled drug product; PD, pharmacodynamic; PK, pharmacokinetic; R, reference (product), e.g., innovator or original product; T, test (product), e.g., a generic or modified product; UF, University of Florida

inhalers (MDIs) and dry powder inhalers (DPIs), including new/innovator and generic/follow-on products. The conference was characterized by its focus on regulatory approaches for obtaining market registrations and by the wide geographic scope at the center of conference discussions. Participants learned about regulatory situations in the US, European Union, Brazil, China, and India; debated designs and interpretation of the pharmacokinetic (PK) and pharmacodynamic (PD) trials of generic inhalers; discussed *in vitro* testing and acceptance criteria for bioequivalence (BE) demonstration; and considered human factor testing of ODPs, which are a combination of a drug formulation and a delivery device that needs to be actuated by a patient when administering a dose.

In addition to the formal podium presentations and panel discussions, the audience actively contributed to the interactive exchange of ideas and perspectives. Overall, over 200 individuals from over 20 countries attended the conference. About 80% of all attendees were from the orally inhaled drug industry, representing 58 companies; 5% were from academia, about 7% from regulatory agencies. The rest of the attendees were consultants, press, and support staff, including several UF students with an interest in inhalation drug delivery design and testing.

A series of in-depth reports from the different sessions of the conference are presented in this theme issue of the AAPS Journal for the benefit of the wider international scientific, academic, and regulatory communities with an interest in inhalation drug products. The following review papers in this issue provide an integrated view of talks and discussions related to a given topic:

- Regulatory considerations for approval of generic inhalation drug products in the US, EU, Brazil, China, and India (by Sau Lee *et al.*) (1)
- Inhalation devices and patient interface: human factors (by Stefan Leiner *et al.*) (2)
- *In vitro* testing for orally inhaled products: developments in science-based regulatory approaches (by Ben Forbes *et al.*) (3)
- Pharmacokinetics of orally inhaled products (by Guenther Hochhaus *et al.*) (4)
- Pharmacodynamic studies to demonstrate bioequivalence of oral inhalation products (by Leslie Hendeles *et al.*) (5)

In addition, results of original research reported at the conference are presented in the following articles in this AAPS Journal issue:

- Application of the modified chi-square ratio statistic in a stepwise procedure for cascade impactor equivalence testing (by Ben Weber *et al.*) (6)
- Effect of device design and formulation on the *in vitro* comparability for multi-unit dose dry powder inhalers (by Jag Shur *et al.*) (7)
- *In vitro*, pharmacokinetic, pharmacodynamic, and safety comparisons of single and combined administration of tiotropium and salmeterol in COPD patients using different dry powder inhalers (by Stephen Horhota *et al.*) (8)

- Safety of β_2 -agonists in asthma: linking mechanisms, meta-analyses, and regulatory practice (by Sanjeeva Dissanayake) (9).

In this overview article, we provide a succinct summary of discussions at the conference. Original presentations and program are also available on the conference's website (10).

REGULATORY APPROACHES IN DIFFERENT WORLD REGIONS

Generic medicines aim to provide more affordable, yet still safe and efficacious, high-quality alternatives to the previously approved innovator drugs. To obtain marketing authorization, the sponsor must provide to the pertinent government agency appropriate documentation about the drug's composition, manufacturing facilities, and other details helping to document and ensure the high quality of generic alternatives. Being a follow-on to a previously approved innovator drug, generics typically have an abbreviated set of data demonstrating equivalence of the generic product to a previously approved product. To that end, the generic drug sponsor must demonstrate equivalence of the proposed generic to the innovator drug through *in vitro* and/or *in vivo* studies. Both designs and results of these studies must be provided to the relevant agency for review, assessment, and approval. The types of studies, acceptance criteria, terminology (e.g., "bioequivalence" vs "therapeutic equivalence"), the overall approach, and even exact definitions of what constitutes a "generic" drug vary by the country. For example, in the U.S., the Food and Drug Administration (FDA) developed a "weight of evidence" approach, whereby equivalence in *all* categories of interest is required for a proposed generic drug to be approved, namely: quantitative and qualitative sameness of the formulation, similarity of the delivery device, *in vitro* performance and *in vivo* performance equivalence. By contrast, in the European Union, regulatory authorities follow a "stepwise" approach, whereby approval could be granted at the *earliest step* in a decision tree where equivalence is demonstrated, starting with *in vitro* equivalence, pharmaceutical equivalence, followed by lung deposition equivalence, systemic PK, efficacy, and, finally, safety PD equivalence. Thus, approval based on "*in vitro* only equivalence" is possible in the EU but not in the US.

Countries also differ in their legal systems and regulatory structure; and each country has its own system of government oversight for the registration and distribution of medical products on its territory. In the case of the European Union, in addition to each country's national governments, the Union's governing bodies provide supra-national mechanisms and requirements for ODPs and other drugs.

The specific regulatory bodies and approval considerations in different world regions are described in detail in a separate article in this theme issue (see "Regulatory considerations for approval of generic inhalation drug products in the US, EU, Brazil, China, and India", by Sau Lee *et al.*, AAPS Journal). A summary of specific considerations related to *in vitro* and *in vivo* tests and acceptance criteria in different region is provided in Table I. It is evident that there are some general similarities across regions but also important differences, of which product sponsors need to be well aware.

Table 1. Summary of Regulatory Approaches for Demonstrating Equivalence of Generic (“Test”) to Innovator (“Reference”) Inhaled Product

Test type	US	EU	Brazil	China	India
Qualitative and quantitative sameness of formulation, including inactive ingredients	Qualitative sameness recommended Quantitative differences acceptable if justified by <i>in vitro</i> and bioequivalence tests	Not necessarily required If formulations are not identical, more <i>in vitro</i> testing is required	Same API, same dose Similar excipients and polymorphic profile	Not necessarily required. The regulatory categorization and consequently registration path and approval requirements may differ if formulation is different	No published recommendations
Device similarity	Recommended	Dosage form should be the same (e.g., MDI, DPI) and handling instructions should be similar	Same dosage form (suspension or powder) Similar device handling characteristics, comparable device design	Device may be approved separately from drug; no clear guidance available	Few specifics published. In some cases, devices may differ if performance is comparable (e.g., for aqueous solutions)
<i>In vitro</i> equivalence	Recommended. key tests for DPIs include DPIs include single actuation content (SAC), aerodynamic particle size distribution (APSD), and device resistance	<i>In vitro</i> tests are required as step 1. If these fail to show equivalence, testing may proceed to PK and if needed to PD or clinical studies	Required. (appearance, priming and repriming, total content, APSD or particle/droplet size for nasals, ED, number of doses, spray pattern)	APSD required and may be sufficient but no specific guidance published	Required For aqueous solutions, <i>in vitro</i> alone is sufficient if formulations are essentially similar and device performance comparable
Pharmacokinetic (PK) equivalence	Used to demonstrate equivalent safety Separate studies for each strength of a multi-strength product Healthy volunteers 90% confidence interval of the geometric mean ratio of AUC and C_{max} must fall within 80.00%–125.00% Research is ongoing to determine whether PK could be used for regulatory demonstration of equivalent efficacy in some situations.	Required for generics unless waiver obtained If PK fails but PD or clinical studies show equivalence, product may be approved as “hybrid” Healthy volunteers (with justification) or patients Use charcoal as appropriate	Required, for both safety and efficacy For efficacy studies, use charcoal if necessary 90% confidence interval for test/reference ratios of AUC_{0-t} and of C_{max} must be within 0.8–1.25 for both safety and efficacy studies	Required unless bioequivalence obtained. Single dose Must be conducted on Chinese subjects/patients, either in China or as part of a global study with a separate analysis on Chinese subjects/patients Currently no specific guidance on use of patients vs healthy subjects	Currently insufficient for approval, but PK-only application for “interchangeability” may be attempted with justification Must be conducted in India; women are typically excluded
Lung imaging	Inadequate for demonstrating BE	May be acceptable to demonstrate equivalent lung deposition Used if PK fails or impractical Cross-over or parallel design accepted Any marker reflective of inflammation may be acceptable as endpoint	Inadequate for demonstrating BE	May be used to prove equivalent local drug deposition	No published recommendations
Pharmacodynamic (PD) equivalence	Recommended, preferred over clinical end-point studies Dose–response required	May be used if PK is not possible (e.g., due to lack of assay sensitivity) Dose–response required for biomarker Two doses of Reference product must be used	Required unless bioequivalence or bronchoprovocation for bronchodilators For ICS, currently no guidance on efficacy endpoints. For safety, use	Required unless BE is self-evident (e.g., aqueous solutions) Cross-over or parallel design accepted Non-responders should be excluded	Required unless BE is self-evident (e.g., aqueous solutions) Cross-over or parallel design accepted Non-responders should be excluded

Table I. (continued)

Test type	US	EU	Brazil	China	India
Clinical end-point trials	Could be used in place of PD	Used if PK and PD fail or impractical	Patients or healthy volunteers 90% confidence interval of the PD response ratio for T/R must be between 0.8 and 1.25. Other limits can be accepted with proper justification Test product must be not worse than Reference with regard to changes in vital signs, biochemical parameters and frequency of adverse events May be used if PK is not possible (e.g., due to lack of assay sensitivity) Dose-response required for biomarker Two doses of Reference product must be used Use patients (e.g., for bronchoprotection) or healthy volunteers	hormones (such as 24- urinary cortisol) Must be conducted in China	Acceptance range on a case-by-case basis; PK criteria may not be used for PD Must be conducted in India by a duly registered CRO
Pediatric equivalence	No separate recommendations published	Some European countries require separate pediatric trials to demonstrate equivalence; others require bridging child-to-adult studies, and yet others have no special BE requirements for pediatric indications	No separate requirements published	Required unless biowaiver obtained Must be conducted in China	Required if there are no appropriate PD measures Cross-over or parallel design accepted Acceptance range on a case-by-case basis Must be conducted in India by a duly registered CRO
Statistical methods	Population bioequivalence for <i>in vitro</i> tests Methods for APSD comparison still under discussion	Average bioequivalence for <i>in vitro</i> tests Default acceptance criteria: $\pm 15\%$	Population bioequivalence for <i>in vitro</i> tests Methods for APSD comparison still under discussion Average bioequivalence approach could be accepted, depending on the data provided by the test Confidence intervals on relevant ratios for <i>in vivo</i> markers	No details available	Average bioequivalence for prescribability Individual bioequivalence required for switchability Limited experience, hence no guidelines for population bioequivalence

The disparities among international regulatory approaches suggest that there are ample opportunities for the regulatory and scientific communities around the world to collaborate to develop a more consistent, better aligned, science-based approach for evaluation and approval of innovator and generic OIDs.

IN VITRO AND DEVICE CONSIDERATIONS FOR DEMONSTRATING BIOEQUIVALENCE

OIDs present unique challenges for *in vitro* testing and characterization of the aerosol cloud generated and delivered by these devices. The drug dose delivered to the patient is a transient bolus of material constantly changing during the path from the inhaler to the deposition sites in the lungs. At the Orlando Inhalation Conference, the scientific and practical challenges of *in vitro* testing of OIDs were considered from two perspectives: (1) the fundamental science that underpins understanding of inhaled drug delivery and the subsequent fate of drugs inhaled into the lungs, and (2) current and emerging methods for *in vitro* testing and their application. The conference presentations and accompanying review article (see “*In vitro* testing for orally inhaled products: developments in science-based regulatory approaches” by Ben Forbes *et al.*) discuss techniques used to assess aerosol deposition, as well as some of the factors that may impact the ability to predict the drug absorption after aerosol delivery, such as particle dissolution, permeation, particle clearance, and tissue exposure. The ability to determine an *in vitro/in vivo* correlation for OIDs with various laboratory techniques remains one of the important areas for the ongoing discussion and research.

The capability to accurately measure and characterize OIDs with *in vitro* test methods provide tools for establishing quality criteria for the development and regulation of both generic and innovator products. The above-mentioned article explores how companies and regulatory authorities are currently using *in vitro* methods to understand the formulation and device and to establish product quality. Some of the current debates about these test methods, their application, the statistics used to evaluate the data, and how all this can lead to a complex regulatory situation are also explored. It is clear from the conference that analysis and interpretation of *in vitro* data are increasingly important for decision-making. The article identifies a number of areas for further work to help achieve the objective of moving *in vitro* tests from a descriptive nature to methods that can measure product performance against objective criteria.

An additional area of complexity for OIDs relates to the device delivering the drug to the patient. The discussion on *in vitro* test methods at the conference was complemented by a number of talks about challenges of device design and studying the device/patient interaction through human factors studies (2). That review article explores the importance of human factors analysis in the design process for OIDs, the challenges which device design presents within a drug product development process, the impact of device changes during the product lifecycle from both technical and regulatory perspectives, and the difficulties of correctly using the inhalers as experienced by some patients.

Both of the referenced articles provide a practical state-of-the-art summary of the current challenges within these areas and a discussion of how techniques may be improved in the future.

IN VIVO (PK, PD, AND CLINICAL ENDPOINT) CONSIDERATIONS FOR DEMONSTRATING BIOEQUIVALENCE

Pharmacokinetic and pharmacodynamics studies are often components of OI DP bioequivalence studies to ensure equivalence in safety and efficacy between test (T) and reference (R) inhalation products. The goal of these studies is to ensure that the pulmonary and systemic exposure (rate and extent of drug availability at the site of action and in the systemic circulation) are confirmed in an *in vivo* situation. Several regulatory agencies continue to put strong emphasis on such *in vivo* tests because *in vitro/in vivo* correlations (which are necessary for using *in vitro* assessments as substitute for *in vivo* studies) are not yet fully developed for OIDs.

The PK- and PD-related presentations at the Orlando Inhalation Conference and the accompanying review articles (“PK studies to support development and approval of generic inhaled products”, by Guenther Hochhaus *et al.*, and “PD studies to demonstrate safety and efficacy of inhalation products”, by Leslie Hendeles *et al.*) discussed a wide range of key topics, such as:

- Optimizing design of PK studies (e.g., healthy volunteers vs patients; training to optimize inhalation techniques);
- Evaluating the relevance of PK and PD studies for systemic as well as pulmonary equivalence testing;
- Identifying *in vitro* parameters relevant for *in vitro/in vivo* correlations;
- Evaluating the sensitivity of PD studies for OIDs;
- The need for harmonizing the conclusions that regulators may draw from PK studies, especially distinguishing systemic vs pulmonary fate of the drug.

Most of the participants at the Orlando Inhalation Conference agreed that PK studies in healthy volunteers are the most sensitive *in vivo* method for assessing equivalence of systemic exposure. More importantly, the majority of participants seemed to agree that given a suitable study design (e.g., charcoal treatment for drugs that are orally available), PK results may enable comparisons of the rate and extent of respiratory drug delivery between T and R formulations.

Effects of batch-to-batch *in vitro* variability of T products on PK BE assessments was identified as an important topic for careful consideration and further research. The need for PK study designs that would allow assessment of intra-subject as well as inter-batch variability was stressed by the U.S. FDA, as this would allow incorporation of statistical methods that adjust BE acceptance criteria for the reference batch variability. As current *in vitro* studies do not seem to capture all properties affecting pulmonary fate of drug after inhalation, PK studies could be employed to obtain all relevant BE properties, such as available dose, equivalent pulmonary residence time, and central/peripheral deposition ratio.

Presentations and discussions also addressed challenges associated with PD approaches to evaluate pulmonary and systemic BE of inhalation drugs. A particular challenge in this area is the lack of dose–response relationships for pulmonary effects of corticosteroids, including the insensitivity of biomarker studies, such as reduction of nitric oxide and airway responsiveness to adenosine for anti-inflammatory effects of corticosteroids. The OIDP experts gathered in Orlando came to the general conclusion that the currently available biomarkers for assessing pulmonary corticosteroid effects are not sensitive enough for BE studies using the dose-scaling approach. Within this context, it was also questioned what information could be drawn from parallel, single-dose clinical study designs proposed by the FDA for fluticasone propionate/salmeterol xinafoate combination formulations, which would compare potential differences on the effect-scale using doses that are close to the upper end of the E_{max} scale and are therefore always likely to pass as long as generic companies are able to afford such studies with large numbers of patients.

An 18-h area under the cortisol concentration time curve was recommended by some for determining equivalent systemic exposure of corticosteroids, while others strongly believed that PK is the most sensitive method addressing the systemic exposure of all inhaled drugs, including short- and long-acting beta-2 adrenergic drugs. This questioned the current thinking of the European Medicines Agency, which allows approval via PD BE studies for systemic exposure by monitoring cortisol, heart rate, serum potassium, and serial electrocardiograms when BE is not established by PK studies.

SUGGESTIONS FOR FUTURE RESEARCH AND DISCUSSIONS

Overall, Orlando Inhalation Conference demonstrated the shared high interest in sound scientific approaches to the development and regulation of inhaled products. The presentations, panels, and audience discussions also highlighted a number of areas that merit further scientific research as well as a public clarification of the underlying principles and practical considerations. An illustrative list of such areas for further exploration is compiled below. Some of these issues may be approached differently by different countries and thus could be beneficially explored through international workshops to aid in global harmonization; while other issues should be further researched in clinics and laboratories through well-designed and subsequently published studies, in order to inform both drug development and regulatory policy.

1. What is the purpose of generic drug testing in a given world region? (And what should it be?) For example, is the goal to demonstrate identical performance or non-inferior performance of the test product compared to reference product? What weight should be given to *in vitro* performance vs *in vivo* performance? Which *in vitro* and *in vivo* tests are most relevant, keeping in mind the above-mentioned overall goal of generic drug testing in a given world region?
2. Given the current diversity of legal, regulatory, cultural, and other aspects, as well as still-open

scientific questions such as *in vivo in vitro* correlations or predictive biomarkers, to what extent could regulatory approaches across different geographic regions be harmonized, and what would be the path to harmonization?

3. Which *in vitro* metrics correlate to which *in vivo* metrics? Under what conditions does each correlation hold? How universal is each observed correlation across different product types?
4. What statistical approaches should be used to compare Aerodynamic Particle Size Distributions (APSDs) of the test and reference products, and what acceptance criteria should be applied?
5. Does testing of dissolution of inhaled drugs provide information relevant to determination of bioequivalence that cannot be obtained from testing other attributes with established methods?
6. What PK study designs could be used to compare regional lung deposition (peripheral and central) between test and reference products?
7. Drug delivery from a DPI may depend on the air flow rate generated by the patient or employed for *in vitro* tests. How exactly should the flow rate dependency be accounted for when comparing test and reference products?
8. How exactly should statistical approaches take into account the batch-to-batch variability of the reference product? How should such evaluations be balanced with the resources expended for testing? Should different acceptance criteria apply to drugs intended for acute use vs chronic use?
9. Does a patient's interaction with an inhaler device have a role in generic drug review, and if so, how should such patient/device interaction be tested and assessed?
10. How can both patients and health-care providers be educated on the correct inhalation technique, which is necessary for appropriate drug delivery and for minimizing variability in clinical trials? How can such an education be provided to patients outside the clinical studies and considering also that they may be using several different inhalers in parallel?
11. What PD/clinical study designs are most appropriate (i.e., sufficiently sensitive, discriminatory, and clinically relevant) to demonstrate bioequivalence of inhalation products? How should different patient populations and different therapeutic indications be represented in generic drug testing?

CONCLUSIONS

The 2014 UF/IPAC-RS Orlando Inhalation Conference attracted a diverse audience from around the world to discuss current approaches and challenges in developing generic OIDs and demonstrating their equivalence in quality, safety, and efficacy to the innovator drug products. The conference highlighted general areas of alignment but also identified the need to:

- develop relevant *in vitro/in vivo* correlations, as current *in vitro* methods are not able to predict *in vivo* performance for OIDs;

- evaluate whether additional *in vitro* tests (e.g., dissolution tests) are necessary or relevant for the intended purpose;
- evaluate the use of PK for assessing the pulmonary fate of deposited drug (e.g., pulmonary available dose, pulmonary residence time, central to peripheral deposition) for slowly dissolving drugs;
- continue international regulatory discussions about whether PK studies are sufficient for making equivalence decisions on systemic exposure; and
- understand best ways to study human factors and device/patient interactions, both for new and generic drugs.

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