CROSS-INDUSTRY *Organizations*

ISAM 2013 Congress Symposium on *In Vitro/In Vivo* Assessment of Inhaled Drugs: Science and Regulatory Issues for Consideration

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On behalf of the International Society for Aerosols in Medicine

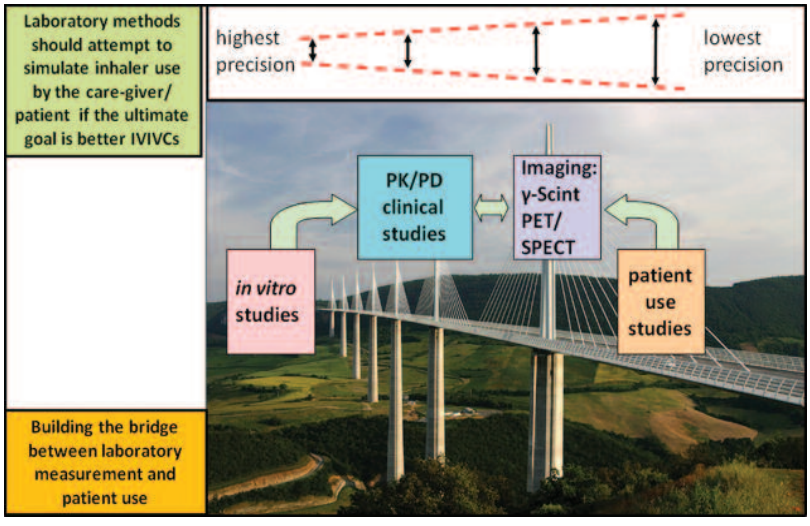
The 2013 ISAM Congress at the University of North Carolina at Chapel Hill included a pre-Congress symposium entitled "Enhancing Accordance between Outcomes of Laboratory and Clinical Testing of Orally Inhaled Drug Products." The program for the April 6, 2013 meeting, developed by the ISAM Regulatory Affairs Networking Group, was intended to provide an up-to-date summary of progress being made in the laboratory as well as in clinical evaluations of orally inhaled drug products (OIPs). The overall objective was to hold a multidisciplinary discussion for enhancing the clinical utility of laboratory tests for possible use as surrogates for *in vivo* performance markers in regulatory submissions. The faculty was comprised of five regulators (three from the US Food and Drug Administration (FDA), one from Health Canada and one from the European Union), two speakers from academia (one of whom was also a regulatory adviser) and six from industry (including one former regulator). In addition to the faculty, more than 60 attendees participated in the discussion sessions, indicative of the level of interest that exists in this topic.

I. Current Status and Challenges

The first of four sessions focused on defining the laboratory test methods, including deposition imaging, that are applicable for bridging the *in vitro/in vivo* gap. There is a broad consensus within the US, Europe and Canada as to the tests that are required and their purposes. Tests such as spray pattern and plume geometry for pressurized metered dose inhalers (pMDIs), though helpful in product development and required for documentation on bioequivalence (BE), are secondary in relevance to *in vivo* performance, compared with drug content per actuation (dose con-

Figure 1

The bridge linking laboratory measurements to patient use investigations via pharmacokinetic (PK) studies, pharmacodynamic (PD) studies and lung imaging methods such as planar scintigraphy (2-D), positron emission tomography (3-D PET) and single photon computed emission tomography (3-D SPECT).



tent uniformity (DCU)) and aerodynamic particle size distribution (APSD). The latter provides information about the sub-fractions of the dose in relation to particle aerodynamic diameter, the correlation of which with *in vivo* particle deposition is uncertain.

In vivo lung deposition is most effectively determined by a range of scintigraphic imaging techniques, including planar (2-dimensional) and single-photon emission computed tomography (SPECT) (3-dimensional) imaging utilizing low gamma-emitters. Positron emission tomography (PET) is also an important 3-dimensional imaging technique and has the additional advantage of being able to assess regional lung uptake of a PET-labeled pharmaceutic. PET, which is used mainly for diagnostic imaging in oncology patients, is widely available at more clinical nuclear medicine facilities than is SPECT. While not required by North American regulatory agencies for a submission package, these imaging methods may enhance the information provided from laboratory and clinical testing outcomes, in particular pharmacokinetic (PK) data, especially when implemented with charcoal to block gastrointestinal absorption and pharmacodynamic (PD) data (Figure 1 and Table 1).

There is currently a disconnect between outcomes from laboratory testing and *in vivo* techniques, a main reason being that the compendial methods utilized are over-simplified representations of the respiratory tract environment as well as lung geometry. The enhancements of laboratory testing apparatuses and procedures to achieve greater representation of respiratory tract geometry are

Table 1

Documentation for bioequivalence: Current regulatory status

	Region	
Parameter	**USA Canada**	**Europe**
In vitro methods	An independent and stand alone *in vitro* element of the "Weight of Evidence" for BE of pMDIs and DPIs. Does not obviate the requirement for acceptable comparative systemic exposure and pharmacodynamic/ clinical performance.	First step in the "Step-Wise" approach for BE of pMDIs and DPIs. With acceptable validation, *in vitro* data alone can be sufficient for documentation of BE.
	Sole evidence for BE for nebulized solution formulations and certain suspension products	
In vivo imaging-lung deposition	Not applicable	Supportive data
Pharmacokinetics (systemic exposure)	A part of the *in vivo* element of the "Weight of Evidence" for BE of pMDIs and DPIs. Does not obviate the need for acceptable comparative *in vitro* performance and pharmacodynamic/ clinical effects.	Second phase of the "Step-Wise" approach for BE of pMDIs and DPIs. It can itself be sufficient for documentation of BE, with no further pharmacodynamic/ clinical evaluation.
Pharmacodynamics	A part of the *in vivo* element of the "Weight of Evidence" for BE of pMDIs and DPIs. Does not obviate the need for acceptable comparative *in vitro* performance and systemic exposure.	Final phase of the "Step-Wise" approach for BE of pMDIs and DPIs. It can itself be sufficient for documentation of BE.
BE statistics	Population BE (*in vitro* testing), Average BE (systemic exposure) and "Dose Scale" BE (pharmacodynamic studies)	Average BE (*in vitro* testing, systemic exposure and pharmacodynamic studies, with certain exceptions of application of potency determinations for the latter)

summarized in Table 2. Tests considered are the determination of Dose Content Uniformity (DCU) and aerosol Aerodynamic Particle Size Distribution (APSD) for the evaluation of pressurized metered dose inhalers (pMDIs), soft mist inhalers (SMIs), nebulizing systems and dry powder inhalers (DPIs). The signs for improved *in vitro/in vivo* relationships (IVIVRs) have been promising. As highlighted in a recent publication,[2] *in vitro* data obtained from a clinically-appropriate measurement system can yield excellent agreement across three different OIP classes (pMDI, DPI and nebulizer) for a particular drug moiety (budesonide).

Table 2

Considerations in adjusting compendial methods for comparisons with clinical data

Existing Test	Consideration(s) for Enhancement
Dose Content Uniformity (DCU)	Replace Ph.Eur. right-angle induction port with anatomically correct or "idealized" age-appropriate inlet representing oropharynx or nasopharynx
	Interface Dosage Unit Sampling Apparatus (DUSA) with breathing simulator to mimic age-appropriate tidal breathing (pMDIs + VHC, SMIs, nebulizers) or inhalation maneuver (DPIs)
Aerodynamic Particle Size Distribution (APSD)	Replace Ph.Eur. right-angle induction port with anatomically correct or "idealized" age-appropriate inlet representing oropharynx or nasopharynx
	Use Nephele/Miller mixing inlet[1] to enable cascade impactor to sample aerosol at constant flow rate simultaneously as inhaler experiences age-appropriate tidal breathing (pMDIs + VHC, SMIs, nebulizers) or inhalation maneuver (DPIs) using breathing simulator

II. Current regulatory considerations for *in vitro* performance testing in approval of OIP

The second session provided an opportunity for speakers from each of the regulatory agencies to present answers to the following question: Can we separate the *in vitro* performance of the drug product from that of the device used to deliver it to the patient in the establishment of BE by laboratory testing? The answer was a firm "no," because the two are inextricably linked. All that *in vitro* testing can therefore do is capture the performance of the drug product in the device as a complete system. Currently, the approach for the demonstration of BE for pMDIs and DPIs differs between the US/Canada and Europe (Table 1). In the former, *in vitro* data form part of the "weight of evidence" in support of BE, whereas in Europe, it is possible (though very difficult in practice) to demonstrate BE by *in vitro* data alone as part of a step-wise approach that includes PK and PD studies as second and third stages of the evaluation of comparative performance. Interestingly, in all three jurisdictions, *in vitro* data can be provided as sole evidence for BE for nebulized solutions and some non-metered (nebulized) suspension formulations because these products are approved and marketed without dedicated devices, although companies seeking approval for nebulizer drug products are encouraged to submit their data identifying a nebulizer system(s) to be used for delivery of the aerosol. There is also a lack of harmonization between the population BE approach recommended by the FDA for statistical interpretation of data and the average BE approach favored in Europe. No jurisdiction accepts *in vivo* imaging data of aerosol deposition with or without *in vitro* methods to demonstrate BE.

Besides an update on the current regulatory requirements in the US, the FDA presentations included valuable and much-appreciated discussions on the science-based decisions the agency takes in its current approval of OIPs as well as development of the guidance documents related to these products. Of particular interest is the research at several academic centers sponsored by the Office of Generic Drugs (OGD) to determine factors critical to development and implementation of the OGD guidances for documentation of BE of OIPs. Based on the presentations at this symposium, the Agency's research is focused on the understanding of factors that may influence BE of multisource dry powder inhalers, such as computational fluid dynamic modeling of the way inhaled particles deposit in the human respiratory tract.

III. Clinical considerations: Drug delivery devices and biomarkers

The third session examined clinical aspects of OIP use, focusing on the steps that can be taken to design inhaled delivery systems that are "patient friendly" and the use of clinical biomarkers as additional support for regulatory approvals. However thorough the processes required for demonstration of OIP performance through *in vitro* testing or by PK/PD measurements in trained volunteers may be, the outcomes can be meaningless if the intended patients do not use the OIPs correctly. Non-adherence to the prescribed regimen is also a major problem with the management of chronic diseases, such as asthma and COPD, for which OIPs are prescribed. A strong case can therefore be made for the adoption of human factors engineering to OIP design, as well as making inhalers more ergonomic and intuitive to use, with instructions that are easily readable and understood.

The session also focused on biomarkers used to compare clinical efficacies of OIPs, especially for inhaled corticosteroid (ICS) treatments. With ICS, outcome measures from spirometry, such as forced expired volume in 1 second (FEV_1) are virtually insensitive to incremental changes in dose, particularly when a patients' response is close to the plateau of their dose-response curve. It is therefore difficult to achieve the gold standard of a clearly-defined dose-response relationship for ICS. Sputum eosinophils were presented as the best biomarker of reduced inflammatory response. Other biomarkers that have been investigated with mixed outcomes include responses to inhaled allergens, fraction of exhaled nitric oxide and mannitol responsiveness. However, the validity of any of the above biomarkers for determining BE requires the demonstration of dose response, which remains to be determined because no such investigation has been conducted using a properly-designed and regulatory-compliant BE study.

IV. Bench to bedside: Linking *in vitro/in vivo*

The final session examined the link from laboratory bench to the bedside of the patient using an OIP, by assessing the role of lung imaging in the development and regulatory approval process and by examining current scientific and regulatory dilemmas associated with OIP evaluation in the context of BE. The assessment of total, but not necessarily regional, lung delivery of OIPs to the patient may possibly be supported by gamma-scintigraphy with the understanding that standardized methodologies must be used for the measurements and analyses that result from these investigations.[3,4] Changes to the formulation, delivery device design and function, and patient interface, as well as the interactions between these variables may be optimized by imaging studies. The toolbox relating the body of *in vitro* performance data to clinical outcomes, whether from imaging, PK or PD studies, is incomplete for OIPs because of missing scientific knowledge. Key areas where gaps in our knowledge exist are in the definition of clinically relevant *in vitro* test platforms, selection of appropriate determinants of *in vivo* performance and in quantitative risk assessment that will support a framework of regulatory decisions for BE in a fully rational way across all jurisdictions. For post-marketing surveillance data (and in submissions for second entry products), a key question is: which regulatory paradigm (Europe versus the US and Canada) offers a better balance of efficacy, safety and accessibility to all forms of OIPs? Clues towards a breakthrough in answering this question may come partly from studies of delivery of systemic agents by the inhalation route.

The overall outcome of the symposium and associated discussions provided several suggestions for enhancing accordance between laboratory and clinical testing of OIPs. These considerations include:

- Careful assessment of patient handling of OIP devices in design, testing and use
- Use of anatomically-relevant testing equipment (inlets, breathing simulation, etc.) and physiologically-appropriate (age, disease) testing parameters for the targeted patient population
- Comparable device handling between laboratory and clinical evaluations
- Minimization (or even closure) of the identifiable gaps between laboratory testing and clinical assessments
- A Quality-by-Design approach utilizing a combination of *in vitro/in vivo* studies in product development and computer modeling/simulations

The general sense of both speakers and participants was that implementation of these concepts could greatly improve the correlation between *in vitro* and *in vivo* observations.

Acknowledgments

Invited moderators and speakers including Orest Lastow (MVIC), Prasad Peri (US FDA), Bita Mirzai-Azarm (US FDA), Alfredo Garcia-Arieta (Spanish Regulatory Authority), Eric Ormsby (Health Canada), Benjamin Cox (Team Consulting Ltd., UK), Federico Lavorini (University of Florence, Italy), Param Nair (McMaster University), Sau (Larry) Lee (US

FDA), Glyn Taylor (Scintigraphics, Cardiff, UK), Steve Horhota (Boehringer-Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, US), Anthony Hickey (University of North Carolina at Chapel Hill, NC, US).

References

1. Miller NC. Apparatus and process for aerosol size measurement at varying gas flow rates. US Patent 6,435,004-B1, 2002.

2. Olsson B, Borgström L, Lundbäck H, Svensson M. Validation of a general in vitro approach for prediction of total lung deposition in healthy adults. J. Aerosol Med. Pulmon. Drug Deliv. 2013; 26, in press.

3. Newman S, Bennett WD, Biddiscombe M, Devadason SG, Dolovich MB, Fleming J, Häussermann S, Kietzig C, Kuehl PJ, Laube BL, Sommerer K, Taylor G, Usmani OS, Zeman KL. Standardization of techniques for using planar (2D) imaging for aerosol deposition assessment of orally inhaled products. J. Aerosol Med. Pulmon. Drug Deliv. 2012;25(S1):S10-S28.

4. Dolovich MB and Bailey DL. Positron emission tomography (PET) for assessing aerosol deposition of orally inhaled drug products. J. Aerosol Med. Pulmon. Drug Deliv. 2012;25 (S1):S52-S71.

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