

Refining inhaled product testing: A review

Across the pharmaceutical industry there is a strong drive towards greater efficiency, from faster time to market, through to better manufacturing practice. Over the last decade, the regulatory environment has changed, as exemplified by the introduction of Quality by Design (QbD), but so too have the economics of the market place, with a buoyant generics sector intensifying the requirement for cost-effective production. Extending knowledge and understanding to promote best practice is now a primary concern.

Against this backdrop, analytical tools are currently facing considerable scrutiny: Do they provide relevant information? Are they as productive as possible?

Inhaled product development presents the pharmaceutical industry with some unique challenges. The difficulty of precisely correlating drug deposition behaviour with clinical efficacy, the impact of patient-to-patient variability on drug delivery, and the complex interaction between formulation and device all complicate any move towards a knowledge-driven approach. Better relationships between *in vitro* test data and *in vivo* behaviour (*in vitro-in vivo* relationships - IVIVR) have long been an industry goal, but the current climate clearly adds impetus to the desire for progress.

The pharmacopoeias relating to inhaled product testing have not changed significantly since 2005, with the incorporation of the Next Generation Impactor (NGI), although new monographs for nebuliser testing have been released recently [1]. The intervening years have seen various developments that over the long term could deliver significant improvements in IVIVR. These range from new techniques for data analysis to new equipment for more representative testing. With the United States Pharmacopeia (USP) scheduled to meet at the end of 2011, and plans to re-write the whole of the USP section on inhaled drug testing (section 601), it is useful to reflect on what these new developments have to offer and how inhaled product testing might be refined to meet the need for greater information.

Understanding current practice

The performance of Orally Inhaled and Nasal Drug Products (OINDPs) is principally assessed via dose uniformity testing and the measurement of aerodynamic particle size distribution (APSD). Dose uniformity testing verifies that the quantity of drug delivered is consistent from batch to batch, and, for multi-dose systems, from dose to dose. Particle size information is gathered to confirm the consistency of dose dispersion and gain some insight into likely *in vivo* deposition behaviour.

Dose uniformity testing is relatively straightforward. The device is 'fired' into a sampling apparatus that enables the capture of the measured dose on a filter. The quantity of active ingredient delivered is then determined by further analysis, typically HPLC. The regulators and pharmacopoeias define criteria for success and provide information about suitable testing regimes.

The aerodynamic particle size distribution of inhaled products is measured using the technique of multistage cascade impaction, a method based on size fractionation of the dose on the basis of particle inertia [2]. In simple terms the sample is separated by successively accelerating it through a series of stages. At each stage smaller particles acquire sufficient inertia to break free of the prevailing airstream and impact on a collection surface (see figure 1). The result is a series of size fractionated samples that can be analysed to determine a particle size distribution specifically for the active.

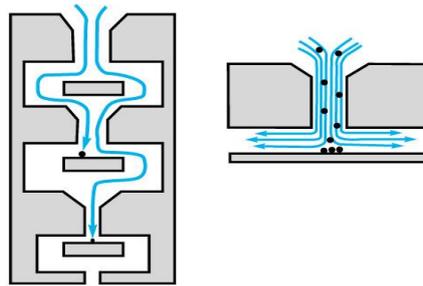


Figure 1: Multistage cascade impaction size fractionates a sample on the basis of particle inertia; smaller and smaller particles collecting on successive stages

Various particle sizing techniques cover the size range of interest for inhalation, but multistage cascade impaction has certain features that make it especially suitable for OINDP characterisation:

- It enables the measurement of particle size information specifically for the active, rather than for the entire formulation, which may include excipients.
- It measures *aerodynamic* particle size distribution (a function of particle shape and density), arguably the parameter most closely correlated with particle behaviour during inhalation.
- It provides detailed resolution in the size range of most interest for inhalation: the sub-ten micron range.

This unique combination of benefits explains the dominance of multistage cascade impaction within inhaled product testing and why it is a mandatory requirement of international regulators. However, while the technique is relied on for the information it generates, its practicalities are less appealing. Cascade impaction can be time consuming and, because it is complex and expensive to automate remains a largely manual technique, increasing the possibility of analytical error.

Scope for change

The drive for greater productivity is stimulating debate as to whether multistage cascade impaction needs to be applied to the extent that it currently is. The two multistage cascade impactors most frequently used are the Andersen Cascade Impactor (ACI) and the NGI. Depending on test set-up these instruments produce either seven or eight size fractions in each experiment, generating detailed APSD information. Over the preceding decades, the number of stages in cascade impactors has risen because of the specific industrial and regulatory requirement for more size distribution detail at various points in the development cycle.

It is now argued by some, that this level of detail is not always necessary to secure effective decision-making. During the early stages of device development, or formulation, for example, Design of Experiment (DOE) studies may be implemented simply to identify parameters that enhance drug delivery and so it may be sufficient to just detect shifts in the fine particle fraction (FPF), typically defined as the sub-five micron dose. Post-production effectiveness in QC depends on an ability to sensitively differentiate between samples and reliably detect one that is out of specification. The argument is that meeting these criteria is crucial – but detailed resolution of the APSD may not be.

Within this context the inhalation community is now actively assessing the merits of abbreviated impactor measurement (AIM).

Abbreviated Impactor Measurement

AIM, as the name suggests, involves characterisation of the emitted dose using fewer size contributions than full resolution multistage cascade impaction: just two or three. It can be implemented in one of two ways: either by grouping the material collected on different stages of a multistage impactor, or by using specially designed equipment such as the Fast Screening Andersen impactor (FSA, Copley Scientific Limited, Nottingham, UK) or the Fast Screening Impactor (FSI, MSP Corp., Shoreview, MN, USA).

Evidence suggests AIM could deliver substantial productivity gains with reductions in overall analysis times of at least 50% [3], but there are also other potential benefits:

- The prospect of higher precision because of the removal of stages on which very little material collects.
- The opportunity to use simpler apparatus that is easier to operate and automate.
- Reduced solvent usage during sample work-up.

These advantages may sound inviting but the crucial question is whether AIM can supply the required information. Can it successfully detect trends in FPF and/or differentiate between closely similar samples?

A study carried out by a group within the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) is a useful starting point for assessment of the AIM concept [4]. In the study Efficient or Lean Data Analysis (EDA/LDA) techniques were applied to existing multistage cascade impaction data for a number of different device types including hydrofluoroalkane (HFA)-solution metered dose inhalers (MDI), chlorofluorocarbon suspension MDIs, HFA suspension MDIs and dry powder inhalers (DPI). The multistage data were grouped into just two fractions which were then used to detect shifts in the APSD.

The study shows that EDA/AIM metrics sensitively detect changes in APSD, providing that the boundary figure segregating the two fractions is set somewhere within the central region of the typically uni-modal, lognormal APSD; sensitivity increasing as the boundary figure approaches the mass median aerodynamic diameter (MMAD) of the formulation.

These findings underpin the twin approaches to AIM that have since evolved: AIM-pHRT (AIM-[potential] Human Respiratory Tract) and AIM-QC [5]. With AIM-pHRT the boundary between the fractions is set on the basis of clinical relevance at five microns, the figure typically used to define FPF. Such systems are configured with an additional stage to separate out the extra fine, sub-one micron fraction, usually considered to be too small to deposit in the lung and therefore exhaled.

In contrast, AIM-QC configurations have a single stage with a cut off as close to the MMAD as the commercial availability of stages allows, to optimise sensitivity. With an appropriately selected boundary, the ratio of the two fractions is able to detect changes in MMAD of the order of just tenths of a micron, indicating that this approach is highly differentiating [4]. Prioritising sensitivity over clinical relevance in this way produces a tool well placed to meet QC testing requirements.



Figure 2: The FSI, shown here with a range of inserts, is based on the design of the NGI pre-separator.

The use of dedicated AIM apparatus, of either type, is still in its infancy but there are now numerous published studies for both the FSA and FSI [6 - 11]. Taken together these show that AIM systems can provide data closely comparable to a full resolution multistage cascade impaction for the majority of OINDPs providing that appropriate test methodologies are applied.

The testing of DPIs has proven most challenging but the latest research suggests significant progress here too [12]. It seems likely that in the relatively near future there will soon be a substantial weight of data demonstrating the ability of AIM techniques to capture trends in APSD and sensitively differentiate between samples.

However, the regulators have yet to formalise the use of AIM and there is a further issue. To swap between full resolution multistage cascade impaction and AIM at different points in the development cycle, the transfer of specifications between the two must be extremely simple, with the preference being for complete parity. Any discrepancies between multistage and AIM data, however well-understood, will inhibit the uptake of AIM techniques and significantly complicate the adoption of a twin track approach.

Better IVIVRs

A parallel and equally important strand in the drive towards greater testing efficiency is the current emphasis on producing *in vitro* data that correlate more closely with *in vivo* behaviour and clinical efficacy. Despite their advantages cascade impactors are not able to precisely simulate the complex flow and particle deposition behaviours that occur in the mouth, throat and lungs [13,14]. This situation is unlikely to change entirely but efforts are underway to modify equipment or practice towards more reliable IVIVRs, to accelerate information gathering.

Developing the inlet port used to connect the device to the cascade impactor during testing is one area of activity; it is widely accepted that the USP/Ph.Eur. induction port does not provide the most accurate *in vitro* realization of aerosol transport through the upper respiratory tract [15]. Developed with testing standardisation in mind the USP/Ph.Eur. induction port has a simple well-defined geometry. It is easy to manufacture and gives consistent performance, both of which are excellent features for QC testing. However, studies have shown that it results in under-prediction of the amount of material captured by the upper respiratory tract [16], highlighting it as one of the causes of imprecise IVIVRs.



Figure 3: The AIT has a more human-like geometry than the USP/Ph.Eur. induction port but is easily manufactured to very close tolerances for consistent analysis

The Alberta Idealized Throat (AIT) is a new piece of testing apparatus (see figure 3) introduced to improve the representation of the impactor/device interface. Developed over the course of a decade at the Aerosol Research Laboratory of Alberta (University of Alberta, Canada), the AIT lies some way between a human throat cast and the USP induction port, thereby combining the advantages of ease of reproducible manufacture and flow rate independent performance with better *in vivo* representation [17]. Early experimental studies with DPis and pMDIs confirm that the AIT captures more of the emitted dose than the standard induction port, more closely replicating measured *in vivo* data [16,18]. Such results support the idea that the AIT may help with the attainment of better IVIVRs, when used with multistage cascade impactors or indeed with AIM-HRT instrumentation.

Also under consideration is the application of more representative breathing profiles during testing. A limitation of cascade impactors is that testing must be carried out at constant flow rate, but this does not mean that the profile applied across the device during testing must be constant too. Mixing inlets effectively de-couple the flow conditions applied to the device and cascade impactor enabling the application of more representative flow profiles [19]. The use of mixing inlets and increasingly sophisticated breath simulators allows inhaled products to be tested under conditions that more closely mimic patient use.

Both of these steps towards better IVIVR focus on better simulation of the delivery of drug to the body but the rate of *in vivo* uptake may also be influential. Several papers, including a USP Stimuli to the revision process, have now been published on the topic of dissolution testing for inhaled drugs, and testing equipment has recently become commercially available [20,21,22]. Because particles delivered to the lung are by necessity extremely fine, there has long been an assumption that they dissolve rapidly, despite the fact that conditions in the lung are far from optimal for dissolution. As OINDPs are used to deliver larger, less soluble drug entities, such as proteins/vaccines, this assumption is being questioned. It may be that in the future dissolution testing becomes more routine as efforts towards better IVIVRs intensify.

Spotlight on nebulisers

Although the pharmacopoeial monographs for the majority of inhaled product testing have not changed significantly since 2005, new guidance has been provided in the area of nebuliser testing [1]. The two new harmonised monographs for nebulisers Ph.Eur. 2.9.44 and USP 1601 which come/come into force in Jan 2012 and August 2011 respectively, provide a useful indication of current regulatory thinking and how inhaled product testing can be refined to give more robust, relevant data.

In the past nebulisers, unlike all other OINDPs, were treated as medical devices and tested independently of the formulation with which they were to be used. The new monographs remove this anomaly, specifying the testing of formulation and device together to properly characterise performance. Other key points are:

- Greater emphasis on use of the NGI because it is the only USP/Ph.Eur. impactor with calibrated performance at the flow rate of interest (15L/min).
- Alignment of the breathing profile applied during delivered dose uniformity testing with the target patient group. The monographs now include four breathing profiles: adult, child, infant and neonate.
- Recognition of the need, in many cases, to cool the NGI to avoid droplet evaporation; an issue that can distort the measured APSD.

In summary, these most recently published monographs provide increased levels of detail, a tightening up of test procedures, and are based on a better understanding of how to achieve more representative data. They focus on selection of equipment that is known to work well under the conditions of interest, the application of patient-specific conditions during testing, and refinement of the test procedure to optimise data quality.

Looking forward

The inhaled product sector is a dynamic one. Pulmonary drug delivery is becoming feasible for increasing numbers of drug entities and the knowledge base relating to device development and formulation continues to grow. However, the mechanisms of drug delivery via the lung and nasal cavity are complex and continue to challenge our understanding. Developing more efficient and relevant testing protocols can only help as the pharmaceutical industry works towards better application of these relatively new technologies.

There have been significant changes since 2005 and the last substantial revision of the pharmacopoeial monographs relating to OINDPs. One important development has been the founding of new industry groups as exemplified by the European Pharmaceutical Aerosol Group (EPAG) and IPAC-RS. With high levels of expert engagement these bodies are working hard towards a better understanding of inhaled drug delivery and the harmonisation of regulation, on the basis of agreed best practice. They have both been active in setting up collaborative studies and publishing data that extends our knowledge in key areas, impactor qualification (stage mensuration and leak testing) and AIM being prime examples, and both are likely to be primary sources of data and information for regulatory revision in the future.

The overall approach to regulation of the pharmaceutical industry continues to evolve, with risk analysis a prime focus. The recent introduction of EMA guidance on the implementation of a risk-based approach to inhaled product testing could influence revisions to the monographs and the FDA is also understood to be planning to update and revise outdated guidance along similar lines in the near future.

The attainment of better IVIVRs is a goal shared by regulators and industry. It enables the faster more efficient development of clinically efficacious products and simultaneously reduces risk. It is also of interest to generic manufacturers seeking to establish improved *in vitro* bioequivalence with reference products [23]. Innovations such as the AIT, mixing inlets and increasingly sophisticated breathing simulators, introduce the possibility of more representative test methods and it will be interesting to see whether they are included in any revised monographs. Clearly the USP and Ph Eur. will need to be convinced that there is sufficient understanding, data and benefit to support a change. The revised nebuliser guidance suggests an understandably keen focus on more representative testing but modifications must be based on secure experimental evidence which can be slow to gather, and a thorough assessment of the practicalities of implementation.

AIM is perhaps the biggest idea to develop in recent years, certainly since the development of the Next Generation Impactor (NGI), and it could potentially transform testing. The practical benefits are obvious but there remains considerable debate within the community about its application. This debate centres on how closely AIM and full resolution impaction data correlate for different device types, most especially DPIs, and the practicalities of applying both techniques at different points in the development/production cycle. Even though collaboration in the area of AIM has been excellent and there is understandable industrial interest in its development the future role of AIM is yet to be clearly defined.

What is clear from all these activities is that there is both appetite and drive to continue to develop inhaled product testing, to enhance productivity and secure better IVIVRs. This bodes well for the development of new inhaled products that meet societal requirements for better, more effective, easier to use pharmaceuticals.

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