



Assessing the Impact of the NGI

A decade after the initial development of the NGI, Mark Copley of Copley Scientific considers its origins and its subsequent impact on the pharmaceutical industry



Mark Copley graduated from the University of Bath in 2000 with a Master's degree in Aerospace Engineering. For the past seven years he has been Sales Manager and Product Specialist for Copley Scientific's range of inhaler testing equipment, and is considered a leading authority in testing methods and systems for metered-dose inhalers, dry powder inhalers, nebulisers and nasal sprays. Mark also provides application support and consultancy, and runs focused training courses and workshops for the inhaled drug testing sector of the pharmaceutical industry. He is a member of the European Pharmaceutical Aerosol Group (EPAG) impactor sub-team, and has made contributions to the Inhalanda working group, leading to subsequent revisions to PhEur and USP monographs.

Cascade impaction data are used to validate the performance of every pharmaceutical inhaled product. Cascade impactor use within the pharmaceutical industry has therefore increased substantially in recent years as the sector has moved to exploit the pulmonary route for drug delivery. Towards the end of the last decade, a consortium of pharmaceutical companies was formed in order to develop an impactor specifically tailored to inhaler particle size characterisation. The result of this collaborative investment was the next generation pharmaceutical impactor (NGI).

Ten years after work began on the NGI, this article examines the criteria used in its development, the key design features of the instrument, and its calibration and performance. Alongside this, the important characteristics of the Andersen cascade impactor (ACI) – the other primary impactor specified in the *US* and *European Pharmacopoeias* for inhalation product testing – are also reviewed. Factors influencing the commercial use of both the ACI and NGI are considered.

DEFINING THE PROBLEM – THE STARTING POINT FOR THE NGI

Cascade impaction is uniquely valuable for inhaled product characterisation because it provides size distribution data specifically for the active pharmaceutical ingredient, rather than for the overall formulation. In addition, it is a technique based on the measurement of aerodynamic particle size diameter, a parameter that is intuitively relevant for inhalation product measurement. A limitation of cascade impaction is its time-consuming and manually-intensive nature.

Before the introduction of the NGI, the ACI was the main impactor used by the pharmaceutical industry. Although originally designed for microbial air sampling, the ACI is a well-established instrument that has served the industry well. It remains in widespread use and is expected to do so into the foreseeable future. One drawback, however, is its configuration, which is poorly suited to automation as a route to improved measurement productivity.

Total analysis time and automation were important issues for the project, and other design criteria were also shaped by limitations associated with the ACI, including:

- ◆ High inter-stage losses
- ◆ Poor stage efficiency and significant stage overlap
- ◆ The lack of good quality, published calibration data

SPECIFYING THE NEW IMPACTOR

Drawing on their extensive experience, the consortium developed a list of 'musts' and 'wants' for the new impactor (1). Some key targets were:

- ◆ A fast manual cycle time (less than 30 minutes) with a design suitable for automation
- ◆ Steep stage collection curves and minimal stage overlap
- ◆ Stages suitable for characterisation in the under 10 micron range, and more specifically a minimum of five stages in the range 0.5 to five microns, across a flow range 30-100L/min
- ◆ Low interstage wall losses – less than five per cent on any stage and less than five per cent overall – to ensure adequate mass balance

The integrity of the new impactor in terms of design, manufacturing quality standards and calibrated performance was also an important issue for the group. The industry wanted a well-defined and documented impactor with recognised performance characteristics.

DEVELOPING THE DESIGN OF THE NGI

The consortium commissioned an acknowledged expert in the air sampling and particle analysis fields to design the new impactor. Interaction between the design team and the consortium was an ongoing feature of the project and at several points alternative options were presented to allow all members an input regarding which solution best served end-user requirements.

Twice in the design process, prototype NGIs were constructed for extensive testing by consortium members, with the results providing important feedback. This approach ensured that the development process generated a design based on state-of-the-art impactor theory that also incorporated the wealth of practical experience within the consortium.

Initial design decisions concentrated on the number of stages and basic layout. Seven stages were finally specified to give five with cut-off diameters in the 0.5-5 micron range, and a horizontal planar layout adopted for ease of operation. Logarithmic spacing of particle cut sizes minimises stage overlap and enhances data interpretation. A detailed aerodynamic design was then developed based on present understanding of impactor theory. Nozzle number, spacing and nozzle-plate distance were all specified to give the required aerodynamic performance – steep collection efficiency curves and well-defined cut-off diameters. Important boundary conditions for optimal design included:

- ◆ Reynolds number through the nozzle should lie in the range 500-3,000
- ◆ Nozzle-to-plate distance should be 1-10 nozzle diameters
- ◆ The cross-flow parameter should be less than 1.2

Cross-flow is a phenomenon whereby the impact from air jets at the edge of the nozzle cluster is inhibited by air flowing from nozzles in the centre. Maintaining the cross-flow parameter below 1.2 avoids this problem.

A layout of the final design is shown in Figure 1. Each circular nozzle assembly is held above a tear-shaped cup in a single seal body. The feasibility of incorporating removable nozzles was considered at some length by the consortium but it was decided that this was not possible without compromising impactor integrity. The current design gives confidence in the jet-to-plate distance – a major determinant of capture efficiency – along with minimising the number of O-rings used and reducing the likelihood of particle accumulation in the nozzle seal-body interface. Perhaps most importantly, it completely eliminates

the risk of the nozzles being replaced in a mixed up way, and thus the potential economic impact of such an out-of-specification event.

A tray holds all the cups, simplifying cup removal, and the impactor assembly is clamped together with a simple handle to ensure leak-free operation. Low inter-stage losses and minimal particle carryover mean that only the cups and tray need changing between tests. Most NGI users purchase multiple cup sets with a single impactor in order to maximise productivity.

At either end the NGI has two larger cups that collect from stage one and the micro-orifice collector (MOC). The design of the stage one cup minimises large particle impaction on the stage walls, while the MOC is a unique feature of the NGI designed to capture the finest particles, eliminating the need for a final glass fibre filter. The impactor also has an optional high-capacity two-stage pre-separator for the removal of oversized particles, a common requirement for dry powder inhaler testing. The induction port itself is single-piece stainless steel component with critical internal dimensions as specified by the *US and European Pharmacopoeia*.

CALIBRATION

To complete the project the consortium invested in an extensive calibration exercise, implemented to an extremely high standard (2). Using an archival NGI, with nozzle diameters close to the specified nominal values, each stage was calibrated at an inlet flow of 30, 60 and 100L/min, covering the full working range of the impactor. The calibration was carried out in accordance with good laboratory practice (GLP) using polydisperse particles. From the resulting data equations were derived which defined the cut-off diameter of each stage under different flow conditions.

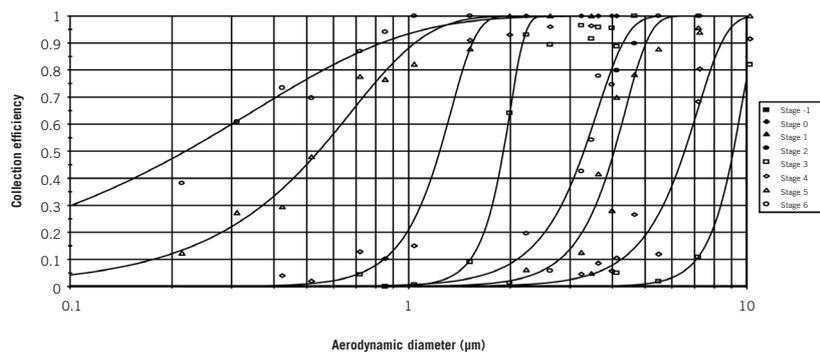
The calibration dataset confirms that the NGI delivers sharp stage efficiencies (see Figure 2a and 2b) with little overlap between successive stages, and provides collection efficiency curves and d50 values (including upper and lower limits as defined by a 95 per cent confidence interval) for each stage. Equations for interpolation between the measured points were also developed to allow confident use of the NGI at any flow rate in the range 30-100L/min.

This 30-100L/min range covers the majority of inhaled product testing; however, for nebulisers and the characterisation of paediatric products, flow rates as low as 15L/min may be required. A further calibration exercise was therefore carried out to assess performance at a flow rate of 15L/min (3). Led by the European Pharmaceutical Aerosol Group, this study shows that at 15L/min stage, cut off diameters for the NGI lie in the range 0.98-14.1 microns, making the impactor suitable for nebuliser characterisation. Some modifications to the NGI are recommended for these applications due to compromised performance at flow rates outside the original design range.

Figure 1: Layout of NGI showing cups and the number and size of nozzles on each stage



Figure 2a: Collection efficiency curves for the ACI (top) and the NGI at 60L/min, illustrating significantly less stage overlap for the NGI



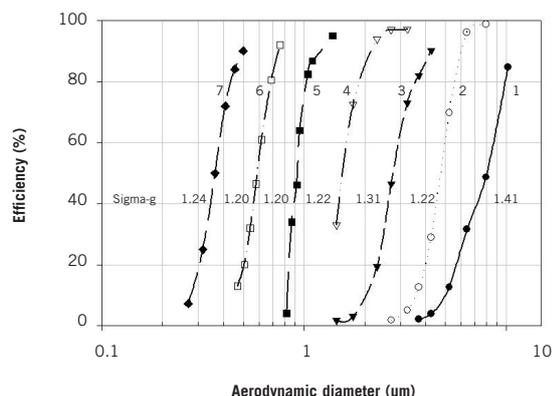
These calibration exercises are an important part of the process put in place to ensure confidence in the NGI. The NGI has measured performance characteristics that derive from a closely specified design; all subsequent NGIs, if manufactured to the strictly defined design specification, will deliver the same performance. Provided that nozzle diameter is verified at manufacture and then regularly checked to assess the effect of wear, no further particle calibrations to assess impactor performance are necessary. This process is called stage mensuration and is a much more cost-effective and less time consuming option than particle calibration.

CURRENT STATUS AND FUTURE OUTLOOK

The NGI is now a well-established tool for the pharmaceutical industry, with around 450 having been sold since launch. Sales of pre-separators, induction ports and cup/tray sets are much higher, indicating the use of multiple components with each impactor. This approach improves productivity, which is typically 50 per cent higher with a manually-operated NGI than with an ACI – an important gain.

Furthermore, a range of labour-saving devices have been developed for use with the NGI. With these devices much of the drug recovery process, including induction port and pre-separator rinsing, is now automatable, further enhancing

Figure 2b: Collection efficiency curves for the ACI (top) and the NGI at 60L/min, illustrating significantly less stage overlap for the NGI



productivity. Twelve or more impaction tests per day is now a realistic goal; a huge improvement compared with the five a day that was the norm before the advent of the NGI.

Process validation, however – a procedure unique to the pharmaceutical industry – produces inertia within the sector. If a product was developed using the ACI then batch release testing is still likely to be carried out using an ACI despite the fact that trials have demonstrated that the two impactors deliver comparable data (4). The same applies to the development of a

generic product based on an expiring patent. In addition, the ACI still offers some advantages for specific applications, in particular its availability in stainless steel and titanium, which offer superior corrosion resistance and ease of refurbishment; individual stages can simply be replaced if worn.

The industry's investment in the NGI has delivered a product that effectively meets its original design brief. Investment in this important tool is ongoing and will focus on addressing any concerns raised by its prolonged use, and in further increasing productivity through automation. In the long term it is likely that the NGI will become the impactor of choice for the vast majority of applications. Change within the industry is, however, slow as a result of the legislation that protects product quality. The ACI, now manufactured to much higher standards than it was originally, is therefore also likely to be in widespread use for many years to come. ♦

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