

# The importance of stage mensuration for cascade impaction

**Why is stage mensuration used in preference to calibration with standardized particles? Measurement systems that deliver the required accuracy are described and there is discussion of how to use mensuration data to assess whether an impactor is fit for purpose.**

Cascade impaction is the primary analytical method used to assess the performance of inhalation products. It permits capture and chemical analysis of different size fractions of a dose, and regulatory authorities recommend its use for the testing of all inhalation formulations and devices. Impactor specifications and test methods are included in both the US and European Pharmacopoeias.

Periodic maintenance and/or calibration, of both the impactor and ancillary equipment, ensures accurate, consistent measurement from the inhaler testing system as a whole. Stage mensuration, which involves measuring the critical dimensions of each nozzle on every stage, is the process used to verify performance, for both new and in-use impactors.

## Controlling aerodynamic performance

Cascade impactors exploit differences in inertia to separate particles within a certain size range. Sample-laden air is drawn through the stages of the impactor, each of which is machined with a number of nozzles with closely specified exit diameters. The diameters of the nozzles and, consequently, overall nozzle area decrease with increasing stage number and accelerate the particle/air stream as it passes through the stages.

Inertia is a function of particle mass/size and velocity. As particles pass through the exit of the nozzle, those with sufficient inertia cross the flow streams and impact directly on a collection surface, while smaller particles remain entrained in the air and pass on to the next stage (Figure 1). As velocity increases from stage to stage, smaller particles acquire sufficient inertia to reach the collection surface. In this way, impactors divide a sample into a number of clearly defined fractions, each of which can be easily analysed to determine chemical composition.

Nozzle exit diameter is a critical parameter for impactor performance. Well-manufactured impactors have cylindrical nozzles, typically with a tapered or trumpet-shaped inlet to reduce inlet losses, but, critically, a sharp nozzle exit with a tightly specified diameter that controls nozzle area, air velocity and, hence, the inertia acquired by the particles. Stokes Law, which is key to impactor theory, can show that the cut-off diameter of any stage is a function of the number of nozzles, nozzle area and the volumetric flow rate of air passing through the impactor. The latter is tightly controlled during testing primarily using high-precision, calibrated flow meters and, in some cases, critical (sonic) flow control apparatus.

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Flow control is a complex subject in its own right and a detailed discussion is beyond the scope of this article. Consistent nozzle dimensions are also vital for accurate measurement.

Cascade impactors are designed to deliver specific stage cut-off diameters, and achieving this performance depends on accurate manufacturing and appropriate maintenance of the instrument. During use, erosion, corrosion and/or occlusion of the nozzles is unavoidable. Effective dissolution of the API often demands the use of corrosive solvents, while the rapid passage of particles through the nozzles inevitably causes wear. The formation of oxidized impurities at the nozzle exit is a commonly encountered cause of occlusion, especially for aluminium impactors, which is why materials such as stainless steel and titanium are now also used.

If the nozzle exit diameter changes, the cut-off diameters of each stage can drift, compromising data integrity and relevance. Any deterioration is detected by stage mensuration.

### Why not calibrate with standardized particles?

Many analytical instruments are routinely calibrated to verify ongoing performance, but this approach is not adopted for impactors. Although impactor calibration with standardized particles is possible, it is time-consuming and potentially error-prone. It is also significantly more expensive than stage mensuration.

One common method for impactor particle calibration uses preformed fluorescent or methylene blue-labelled

monodisperse polystyrene latex microspheres. The particles are supplied in an aqueous suspension and then aerosolized using a vibrating orifice aerosol generator to enable sampling at a fixed flow rate by the impactor. Each sample fraction is then dissolved, releasing the marker. The amount of marker is quantified using luminescence spectrophotometry to determine collection efficiency and a  $D_{50}$  (the diameter at which 50% of the particles are collected) for each stage.

Comparison of these data with design specifications for the impactor allows the detection of any deviation in performance.

Inaccuracies in particle calibration can result from errors in a large number of variables, including calibration particle characteristics, and the accuracy of flow measurement and marker detection devices. Stage mensuration — checking the mechanical dimensions of the impactor against a calibrated specification — is an easier and more effective approach.

Development of the next generation pharmaceutical impactor (NGI) demonstrates how stage mensuration can eliminate the need for repetitive particle calibrations.<sup>1</sup> As part of the design process for the NGI, nozzle size and number were specified to give logarithmically spaced stage cut-off diameters in the required range to study inhalation products. A newly manufactured NGI, with nozzle diameters close to nominal values, was then selected from a routine production batch to be used as an archival instrument. This was calibrated to a very high degree of accuracy, using

polydispersed particles,<sup>2</sup> initially at between 30 and 100 L/min, and then at 15 L/min in a separate study.<sup>3</sup> The NGI defined by the original design specification, therefore, has calibrated performance characteristics and any NGI manufactured to these precise dimensions will, by definition, also deliver that same aerodynamic performance. Reproducible performance is verified by remeasuring nozzle dimensions periodically during use with stage mensuration.

### On the go...

- Regulatory authorities recommend the use of cascade impaction for the testing of all inhalation formulations and devices.
- Cascade impactors deliver specific stage cut-off diameters, and achieving this performance depends on accurate manufacturing and appropriate maintenance of the instrument.
- Effective data interpretation is the link between nozzle diameter measurement and cascade impactor performance.
- Stage mensuration is a cost-effective way of validating performance and regular stage mensuration is the best way to maintain confidence in the integrity of data.

Figure 1 Air flow through an impactor.

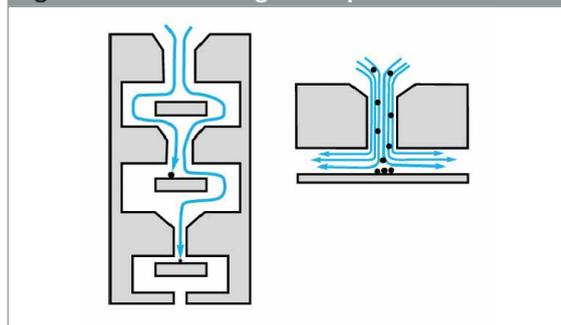


Table 1 Nozzle manufacturing specifications for the ACI and NGI.

Andersen Cascade Impactor (ACI)			Next Generation Impactor (NGI)		
Stage number	Nozzles	Nozzle diameter (mm)	Stage number	Nozzles	Nozzle diameter (mm)
0	96	2.55 ± 0.025	1	1	14.30 ± 0.05
1	96	1.89 ± 0.025	2	6	4.88 ± 0.04
2	400	0.914 ± 0.0127	3	24	2.185 ± 0.02
3	400	0.711 ± 0.0127	4	52	1.207 ± 0.01
4	400	0.533 ± 0.0127	5	152	0.608 ± 0.01
5	400	0.343 ± 0.0127	6	396	0.323 ± 0.01
6	400	0.254 ± 0.0127	7	630	0.206 ± 0.01
7	201	0.254 ± 0.0127	MOC*	4032	approximately 0.070

\* the Micro-Orifice Collector (MOC) is not a particle classifying stage and acts only as a substitute for a final filter

## The practicalities of stage mensuration

Nozzle number and nominal diameter for each stage of the Andersen Cascade Impactor (ACI) and NGI, the two impactors used for the vast majority of inhaler testing applications, are shown in Table 1. Stage mensuration requires systems that can rapidly and accurately measure diameters down to fractions of millimetres.

Automated vision systems are an optimal choice. With these, a light source illuminates the nozzles with transmitted (and in some cases internally reflected) light providing contrast to differentiate between nozzle exit and the surrounding metal. The diameter is determined using the edge detection or pixel count method, or a combination of the two. Edge detection relies on locating a series of points around the circumference of the nozzle exit from which perimeter and diameter are determined.

Conversely, pixel count is an area-based approach. Using a thresholding method, pixels are categorized as either being part of the nozzle area (lit) or part of the surrounding metal (unlit). Those that are part of the nozzle area are counted and the diameter is determined from this measurement.

Accuracy and reproducibility are key if any changes in nozzle diameter are to be attributed to changes in the impactor rather than to variable stage mensuration data. Vision systems with a high degree of automation offer excellent performance in this respect. Illumination of the nozzle is necessary for measurement, but the extent of illumination must be carefully controlled. If the nozzle is over-lit then it will typically be measured as larger than it is, while an under-lit nozzle will be undersized.

Automatic focus also improves measurement accuracy by ensuring a reproducible sharp edge at the nozzle exit plane. Historically, some poorly manufactured impactor stages have shown evidence of a very slight 'bow' (i.e., the stage is not perfectly flat across its entire surface) in which case focus may need to be fractionally altered to maintain sharpness across the stage. Automatic focus ensures that the sharpest images are consistently measured for all nozzles.

Reproducibility is further enhanced

through careful consideration of every aspect of the mensuration process. Temperature control of the surrounding environment is preferable while the use of a curtain can prevent the entry of stray light. Periodic calibration of the system to traceable standards is also essential and is typically performed by a certified external laboratory. This calibration is normally verified on a daily basis using bespoke reference standards, such as glass reticles, to ensure calibration remains robust during routine system operation. The correct positioning and orientation of stages on the vision inspection bed is extremely important and the best operators use special frames to support the stages.

Using a defined system validation procedure, the performance of the Mitutoyo QV404 was evaluated. The maximum diameter deviation noted (99% confidence interval) was 0.00071 mm (0.71  $\mu\text{m}$ ) and the optical reproducibility of the system is, therefore, quoted as 1  $\mu\text{m}$  for the purpose of diameter measurements.

Measuring to this level of precision enhances the integrity of the mensuration process. The smallest nozzle diameter measured during

mensuration is that of stage 7 of the NGI, which is 0.206 mm with a manufacturing tolerance of  $\pm 0.01$  mm. A reproducibility of 1  $\mu\text{m}$  is two orders of magnitude smaller than the nozzle size and equates to only 5% of the available manufacturing tolerance, even

## Cascade impaction data characterizes all inhalation products, making the performance of impactors an important issue for the pharmaceutical sector.

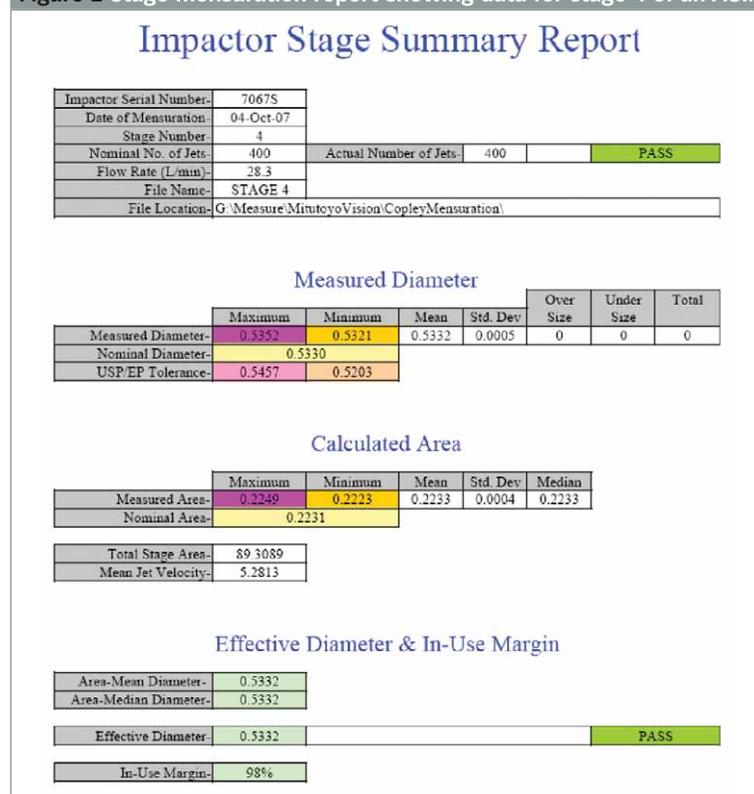
in the worst case. In contrast, less accurate systems may measure to  $\pm 5$   $\mu\text{m}$ , a much greater potential measurement error.

## Interpreting stage mensuration data

With the best optical systems, and closely defined and validated stage mensuration procedures, accurate and reproducible nozzle exit diameter data can be gathered. However, how should the data be interpreted to assess the state of an impactor? Whether it has 'passed' or 'failed', whether it needs maintenance or is suitable for ongoing use?

Effective data interpretation is the link between nozzle diameter measurement and cascade impactor

Figure 2 Stage mensuration report showing data for stage 4 of an ACI.



performance. Two parameters are particularly useful in this analysis: effective diameter and in-use margin.

**Effective diameter.** Theoretical analysis of multinozzle impactor stages has shown that these behave as if all the nozzles are equal in size to an effective diameter.<sup>4</sup> The formula used to determine effective diameter is given: Effective diameter = (area mean diameter)<sup>2/3</sup>(area median diameter)<sup>1/3</sup>. Area mean diameter is back-calculated from the mean value of measured areas for the nozzles on a stage. Area median diameter is an analogous parameter determined from median area.

Stokes Law can be used to relate nozzle diameter and number to stage cut-off diameter. Using this correlation it is possible to determine the stage cut-off diameter that a mensurated stage will deliver, and, more importantly, mathematically compare it with, for example, original performance and/or the design specification for an impactor. The equation below shows how the cut-off diameter of a stage with a measured effective diameter (2) relates to that of a baseline (1).

$$D_{50,2}/D_{50,1} = (\text{Effective mean diameter}_2 / \text{Effective mean diameter}_1)^{3/2}$$

Measuring effective diameter permits quantification of the impact on stage cut-off diameter of nozzle occlusion. As a result, the performance of the impactor can be mathematically correlated with baseline behaviour. This might be the performance of the impactor at the last mensuration or, when new, or the design specification for an ACI or NGI.

**In-use margin.** In-use margin is determined by comparing effective diameter with the nominal diameters and tolerances quoted in the US and European Pharmacopoeias; for example, if effective diameter is exactly equal to nominal stage diameter, the in-use margin is 100%. An effective diameter of 1.212 mm for stage 4 of an NGI, which has a nominal diameter of 1.207 and a tolerance of  $\pm 0.01$  mm, would be equivalent to an in-use margin of 50%. A negative in-use margin indicates a stage diameter outside the pharmacopoeia tolerance.

These parameters are displayed in Figure 2, which shows a summary report for the fourth stage of an ACI. The manufacturing specification for this stage is  $0.533 \pm 0.0127$  mm. The effective diameter calculated from the

measurements performed is 0.5332 mm. Using the equation, the drift in effective diameter will produce a change in stage cut-off diameter of  $<0.1\%$ . The 0.0002 mm drift in diameter has eaten into manufacturing tolerance by only 1.6% and the in-use margin is given as 98%. This impactor is still well within manufacturing specifications.

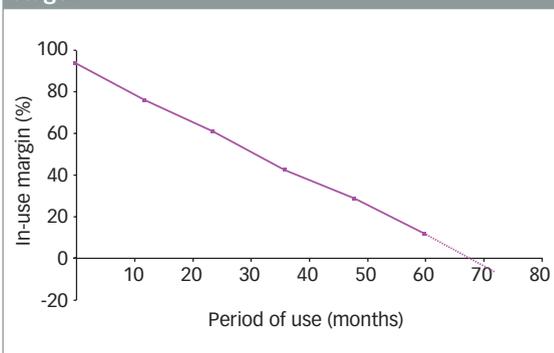
Successive mensuration reports allow the tracking and monitoring of any deterioration of in-use margin, a useful way of investigating how an impactor is wearing with time (Figure 3). This approach allows the likelihood of an out-of-specification stage occurring within the next calibration cycle to be predicted, indicating when remedial work will be required.

### Restoring impactor performance

If stage mensuration results in an effective diameter in excess of an upper limit, then the stage must be replaced. This is a sign that the nozzles have worn — either as a result of corrosion, erosion or physical damage — and there is no further option available as it is not practical to reapply material to impactor nozzles. However, this situation is rare as the vast majority of impactors tend to drift out of specification because effective diameter decreases below the lower limit for the stage. This can be caused by a build-up of hardened particulates or, more likely, because the corrosion process produces metal salts that occlude the nozzle. If the effective diameter is too small, performance can sometimes be improved or restored.

Ultrasonics can be used to clean all impactors prior to mensuration, removing any dirt accumulated during packing, transportation and handling. If the effective diameter is too small, rigorous cleaning may further remove deposits and restore performance. Otherwise, stage pinning is a secondary option. Pushing stainless steel 'go' pins with a diameter between the nominal diameter and the lower tolerance limit for the stage through each nozzle, clears away accumulated debris.<sup>5</sup> This may produce the required effect, as seen in Figure 3, but nozzle damage is a potential risk, particularly for aluminium impactors. The alternative is stage replacement.

**Figure 3** Tracking in-use margin for an impactor stage.



### Conclusion

Cascade impaction data characterizes all inhalation products, making the performance of impactors an important issue for the pharmaceutical sector. Stage mensuration is a cost-effective way of validating performance and regular stage mensuration is the best way to maintain confidence in the integrity of data. State-of-the-art automated vision systems offer unsurpassed reproducibility and accuracy for stage mensuration, producing measurements accurate to within 1  $\mu\text{m}$ . Understanding the correlation between these measurements and impactor performance is key when verifying the performance of a new impactor or assessing whether a used instrument should remain in service. PTE

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