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eBook

An Introduction to Cascade Impaction

Cascade impaction is a core analytical technique for orally inhaled and nasal drug products (OINDPs). Its ability to measure **aerodynamic** particle size metrics for active pharmaceutical ingredient(s) (APIs), as opposed to the entire formulation, sets it apart from other particle sizing techniques and ensures enduring relevance. Cascade impaction metrics quantify critical quality attributes for OINDPs, and compendial methods are applied from R&D through to QC.

For those working with OINDPs a robust understanding of the basics of cascade impaction is key to its effective use. Copley Scientific has been making cascade impactors for over 30 years, and training analysts to use them for just as long. This ebook is a distillation of our expertise, our understanding of what people need to know and the issues that challenge. We hope you find it helpful.

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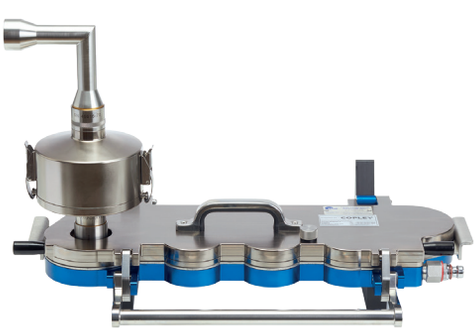
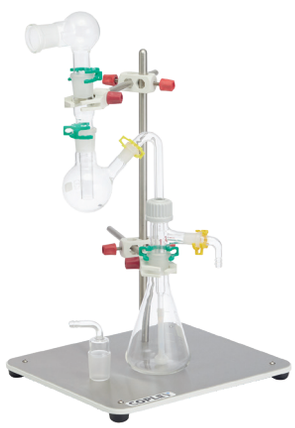


NGI

ACI

MSLI



GTI

I. Know Your Impactor

A short history

By the 1950s, when modern orally inhaled products (OIPs) were first commercialised, impactors were already closing in the on their centenary. Over the preceding decades, a range of designs had been developed to sample airborne particles for applications ranging from epidemiological studies to the protection of industrial workers[i]. With their ability to measure the concentration or mass of particles of specific size, in flowing air, impactors were a natural fit with the informational requirements for OIP development and by the 1970s their potential for sizing drug delivery aerosols was widely recognised. A new and defining chapter in the application of impactors began.

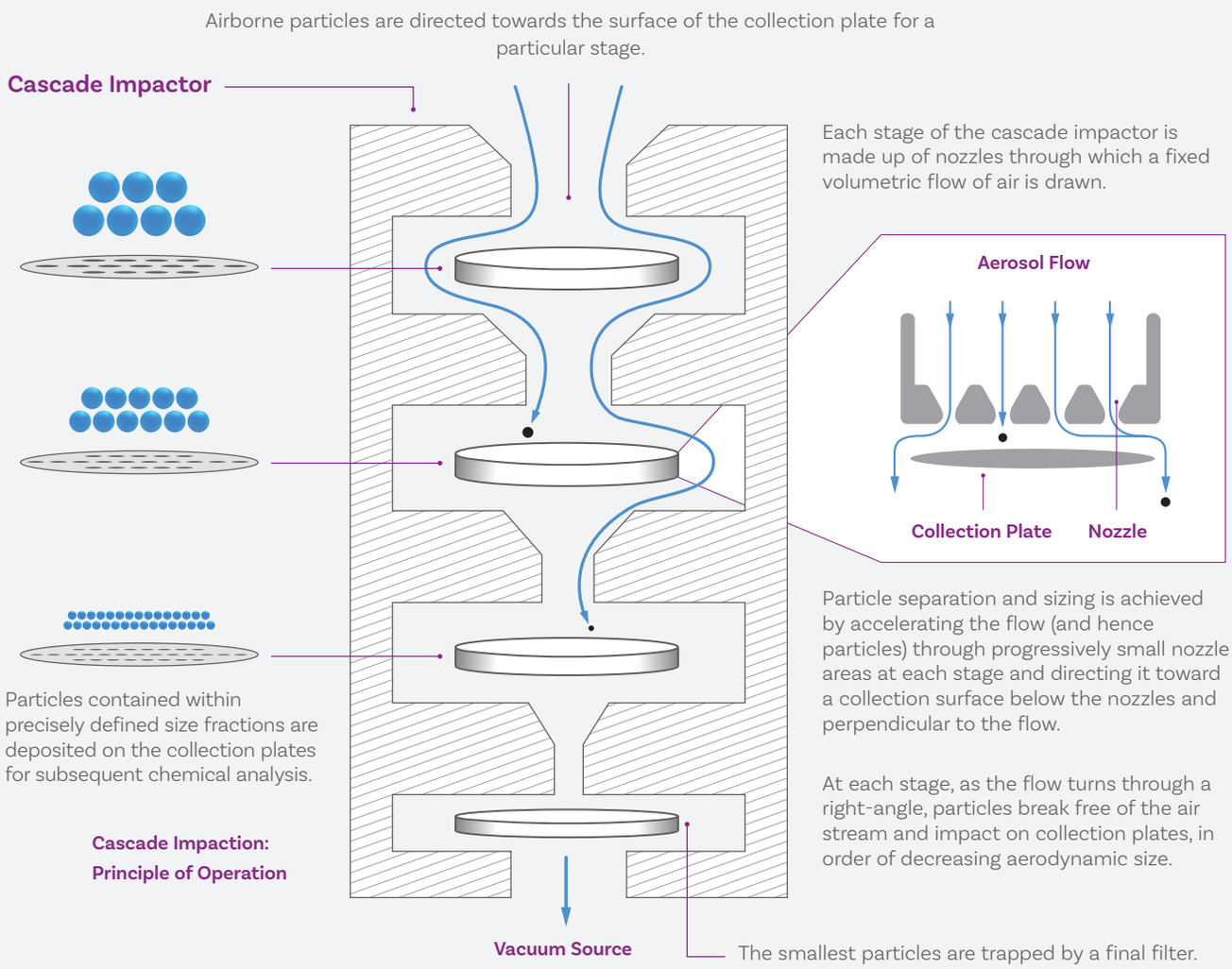
At this time, three of the four impactors in today's compendial methods were already in place: the Glass Twin Impinger (GTI), the Multi-Stage Liquid Impinger (MSLI) and the Andersen Cascade Impactor (ACI). By the 1990s we, Copley, had transformed the manufacturing quality of ACIs, working to well-defined specifications and much improved tolerances to meet requirements for enhanced precision in pharmaceutical applications, relative to preceding applications. However, as activity in the OIP market grew, certain limitations of the ACI became evident, a key issue being productivity.

The industry-led response was to establish a consortium to develop a new multistage cascade impactor specifically for pharmaceutical applications. Building on a robust understanding of aerodynamics and inertial impaction, and of industry needs, this consortium of leading pharmaceutical companies invested significant resource into developing an optimal solution for OIP testing[ii]. The result was the Next Generation Impactor (NGI). Launched in December 2000 the NGI has proven highly successful and together with the ACI it dominates the modern OINDP testing landscape. Improvements in manufacturing over the intervening decades, such as enhanced nickel plating and greater nozzle machining accuracy, along with the launch of the NGI+, with a stainless-steel lid for enhanced corrosion resistance, have only added to the instrument's appeal.

Principles of cascade impaction

The fundamental principles of inertial impaction, which underpin the operation of all impactors, are relatively simple but worth examining, since a robust understanding helpfully informs impactor use.

How Does a Cascade Impactor Work?



A summary of how a cascade impactor works.

Impactors separate particles in a flowing sample on the basis of particle inertia, which is a function of particle mass and velocity. Sample-laden air is drawn through successive stages of the impactor at a fixed volumetric flow rate. Each stage has a defined number of nozzles specified such that nozzle size/total nozzle area decrease with increasing stage number (see table). This means that air, and by extension particle, velocity progressively increases stage-to-stage.

Anderon Cascade Impactor (ACI)		
Stage number	Nozzles	Nozzle diameter (mm)
0	96	2.55 ± 0.025
1	96	1.89 ± 0.025
2	400	0.914 ± 0.0127
3	400	0.711 ± 0.0127
4	400	0.533 ± 0.0127
5	400	0.343 ± 0.0127
6	400	0.254± 0.0127
7	201	0.254 ± 0.0127

Next Generation Impactor (NGI)		
Stage number	Nozzles	Nozzle diameter (mm)
1	1	14.30 ± 0.5
2	6	4.88 ± 0.04
3	24	2.185 ± 0.02
4	52	1.207 ± 0.01
5	152	0.608 ± 0.01
6	396	0.323 ± 0.01
7	630	0.206 ± 0.01
MOC	4032	Approx 0.070

Specifications for the ACI and NGI show how nozzle size/total nozzle area decrease with increasing stage number, thereby increasing particle velocity.

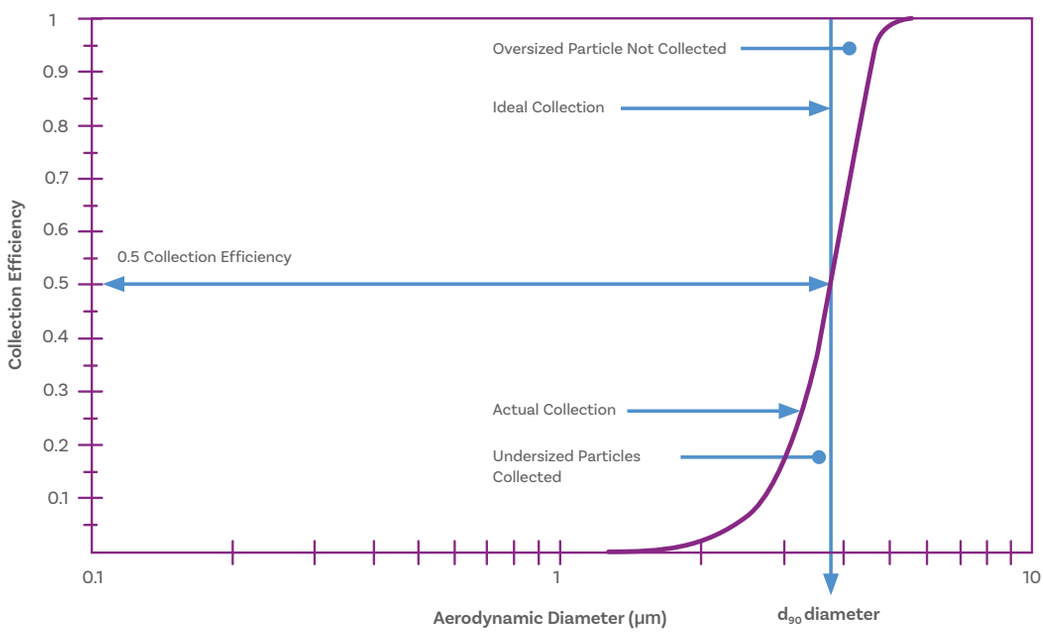
At any given stage, particles with sufficient inertia break free of the prevailing airstream and impact on the collection surface, the rest flow through to the next stage. As particle velocity increases, particles of progressively lower mass attain this 'threshold' value of inertia which means that stage cut-off value – the diameter of particles that collects on a stage – decreases with increasing stage number. In this way cascade impaction produces a series of size fractionated samples. Recovering these samples and subjecting them to suitable assay, typically High Performance Liquid Chromatography (HPLC), produces an aerodynamic particle size distribution (APSD) for the API(s).

This brief description highlights the defining advantages of cascade impaction for OINDPs which are its ability to deliver:

- An **aerodynamic** PSD, metrics of intuitive relevance for inhaled drug delivery.
- Specifically for the **API(s)**, as distinct from the formulation.

No other particle sizing technique combines these valuable characteristics in the size range of interest for inhaled drug delivery. Furthermore, cascade impaction sizes the entire emitted dose, rather than measuring just a proportion of it, an important added benefit.

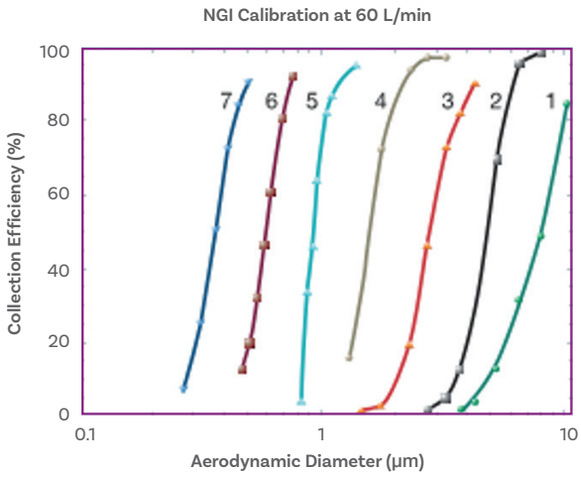
Understanding stage performance: Stage/collection efficiency and stage cut-off diameter



Tightly defined specifications, exemplary manufacturing standards and rigorous practice drive collection efficiency as close to ideality as possible.

In an ideal world, each stage of an impactor would capture particles of a single size (see Ideal Collection line above). In reality, a few undersized particles may be inadvertently collected and some oversized particles may carry through. In other words, ***stage or collection efficiency*** is not 100%.

The ***stage cut-off diameters*** quoted for cascade impactors are the aerodynamic diameter associated with 50% collection efficiency at a ***specific flow rate***. They reveal nothing about overall stage efficiency - the shape of the curve, as opposed to its midpoint - though this is crucial to precision. The fundamental aerodynamics of the instrument, manufacturing tolerances, operational practice and the extent of any change in impactor dimensions - notably nozzle diameter – all impact the collection efficiency curve.



Take a closer look at the performance of the NGI within this context[iii]. Steep stage efficiency curves with minimal overlap between stages are evidence of its excellent separation characteristics.

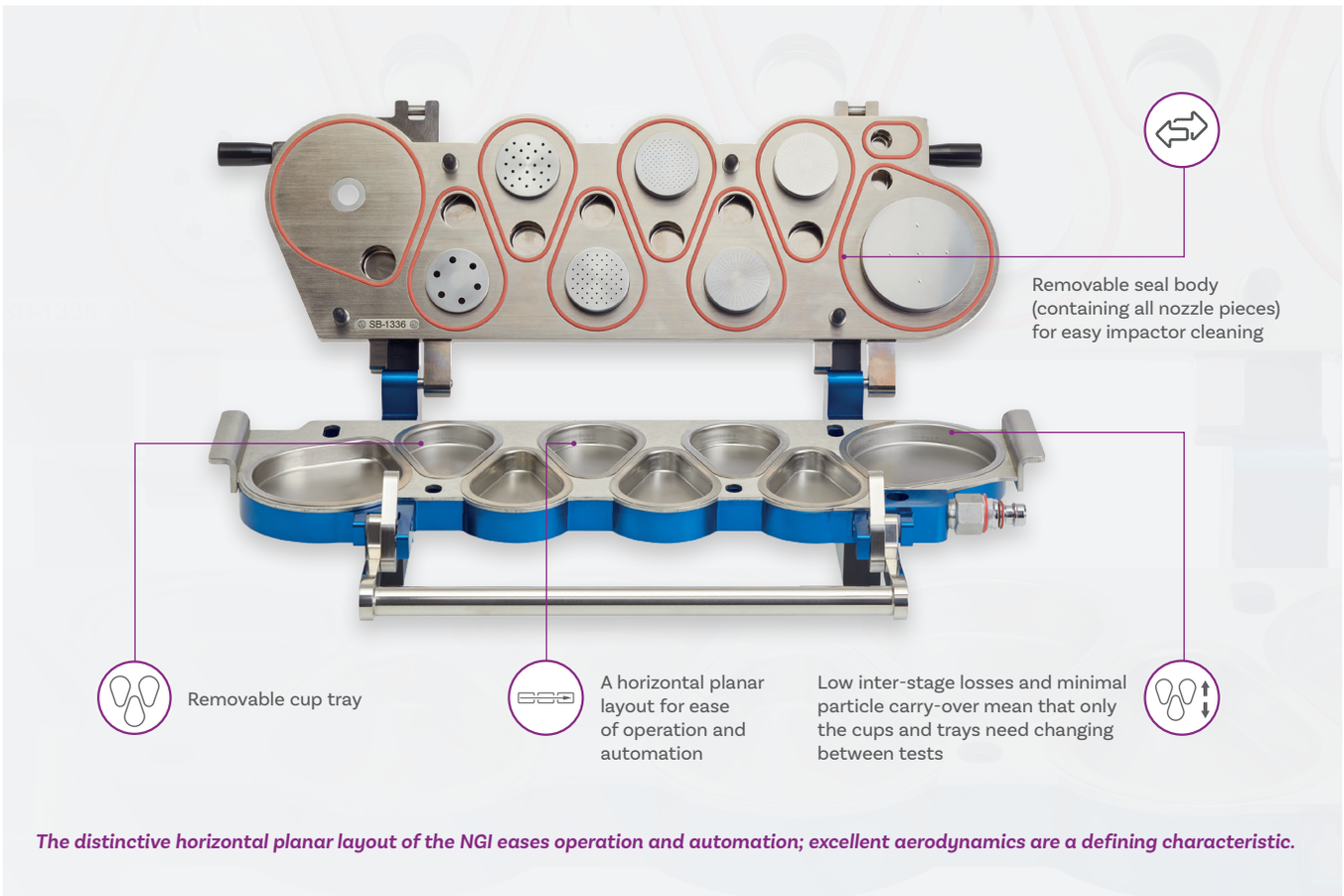
Steep stage efficiency curves with minimal overlap between stages were a key objective in the NGI design; calibration data demonstrate the performance delivered[iii].

Introducing the impactors

Regulatory requirements and/or equipment availability tend to dictate impactor choice, but it is helpful to understand the strengths and limitations of the options for optimal use.

Next Generation Impactor (NGI)

The NGI is a multistage cascade impactor with seven stages plus a micro-orifice collector (MOC) for capturing residual fines. It sizes particles from 0.24 to 11.7 µm (depending on test flow rate) and includes five stages with cut-off values in the range 0.54 to 6.12 µm at test flow rates from 30 to 100 L/min. Available with a nickel plated aluminium or stainless steel seal body, the NGI is suitable for high resolution APSD measurement for all types of OINDPs.



The distinctive horizontal planar layout of the NGI eases operation and automation; excellent aerodynamics are a defining characteristic.

Strengths:

- High productivity: fast manual cycle time (<30 minutes) and amenable to automation.
- Steep stage efficiency curves with minimal stage overlap (see box).
- Low interstage losses, <5% across the impactor.
- Calibrated performance across a wide flow rate range, from 15 – 100 L/min.

Limitations:

- Superior aerodynamics/high jet velocities increase the risk of particle bounce, necessitating effective surface coating for certain formulations.
- Care is required to minimise corrosion particularly when working with lighter weight aluminium models at low temperature and high humidity.

Anderson Cascade Impactor (ACI)

The ACI is a multistage cascade impactor with eight stages and a final filter. Available in stainless steel, titanium or aluminium, it sizes particles from 0.4 to 9 µm (depending on test flow rate) and has eight stages with cut-off diameters in the sub-10 µm range. The ACI was originally designed for operation at 28.3 L/min (1 cubic foot per min), but conversion kits consisting of interchangeable stages are available for operation at 60 L/min and 90 L/min. It is suitable for testing all OINDPs, except nebulisers.

The vertical planar layout of the ACI makes it a small footprint, easy to handle impactor; damaged stages can simply be switched for new.

Strengths:

- Small footprint, due to vertical planar layout.
- Stacked design that facilitates the replacement of damaged stages.
- Good corrosion resistance: material of construction can be matched to formulation chemistry.

Limitations:

- Poorly amenable to automation relative to the NGI.
- No archival calibration data.
- Conversion kits required for operation above 28.3 L/min; unsuitable for operation at lower flow rates.

Multi Stage Liquid Impinger (MSLI)

The MSLI is a four-stage impinger with an additional final filter. Available in stainless steel, titanium or aluminium it sizes particles from 1.7 to 13.0 µm (depending on test flow rate) and is suitable for operation across the flow rate range 30 – 100 L/min. A traditional testing apparatus, it is used mostly for dry powder inhalers (DPIs) and metered dose inhalers (MDIs).

Easy to use, and with no interstage losses, the MSLI can be a good choice for low resolution measurements for DPIs and MDIs.

Strengths:

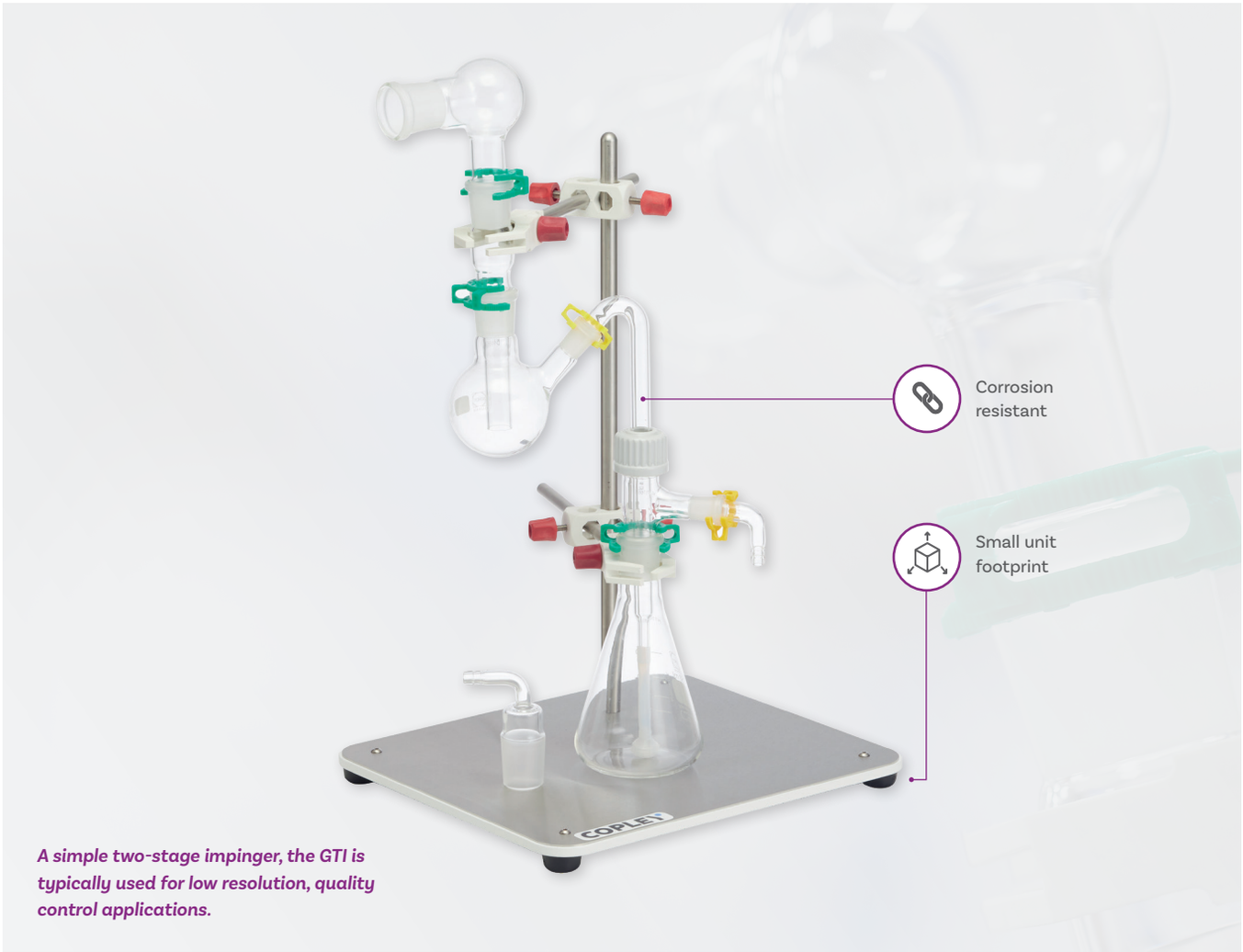
- No interstage losses.
- Moist collection surfaces eliminate particle bounce and re-entrainment.
- Quick and easy to mensurate.
- Good corrosion resistance: materials of construction can be matched to formulation chemistry.

Limitations:

- Relatively low resolution: just four impaction surfaces.
- Minimal opportunities for automation.
- Not uniformly included in all pharmacopoeias.

Glass Twin Impinger (GTI)

The GTI is a simple two-stage impinger that divides the dose emitted from an OIP into 'respirable' and 'nonrespirable' fractions. The particle size boundary is fixed at 6.4 µm at 60 L/min; test flow rate is limited to this value. The GTI is primarily used for routine, relatively coarse quality control, for DPIs and MDIs.



A simple two-stage impinger, the GTI is typically used for low resolution, quality control applications.

Strengths:

- No interstage losses.
- Simple and easy to use, no requirement for regular mensuration.
- Good corrosion resistance: wetted parts are all glass.

Limitations:

- Low resolution.
- Not uniformly included in the pharmacopoeias (see below).
- Can only be operated at 60 L/min limiting relevance for certain products.

Impactor, impinger what's the difference?

An impactor has dry collection surfaces, though they may be coated with a sticky substrate to reduce particle bounce, while in an impinger collects particles in liquid reservoirs, typically in a compatible solvent.

Regulatory requirements

The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) provide general regulatory guidance for OINDPs that includes references to APSD measurement [iv,v,vi]. This guidance is globally relevant because of the size of the markets covered by these authorities and the export appeal of those markets. However, this guidance is not harmonised, notably with respect to generic submissions (see below). Furthermore, the number of country-specific regulatory frameworks is growing as flourishing OINDP sectors establish across the globe. In Brazil, for example, the active inhaled generics sector is regulated and informed by the National Agency for Health Vigilance (Agência Nacional de Vigilância Sanitária, ANVISA) [vii].

When it comes to selecting test methods to support a regulatory submission, common practice is to utilise those specified in the relevant pharmacopoeias - the US Pharmacopeia (USP) for submissions to the FDA, for example, and the European Pharmacopoeia (Pharmacopoeia Europaea, Ph. Eur.) for the EMA. The pharmacopoeias are collections of chapters and monographs for medicines that describe tests to quantify product quality and it is important to note that they operate independently of the regulators. That said, the regulators may directly reference methods in the pharmacopoeias and the use of compendial methods helps to minimise the risk of submitting data that will be judged inadequate.

The general chapters of the pharmacopoeias - notably USP <601> [viii] and Ph. Eur. 2.9.18 [ix] - clearly differentiate commercially available impactors with respect to their utility for different OINDPs.

In summary:

The NGI is specified for all types of OINDP, by all major pharmacopoeias, including USP, Ph. Eur., Chinese Pharmacopoeia (ChP) and Japanese Pharmacopoeia (JP).

The ACI is specified for all types of OINDP, ***except for nebuliser***, by all major pharmacopoeias. This is attributable to the unsuitability of the ACI for testing at the 15 L/min specified for nebulisers.

For the MSLI and GTI the picture is more mixed, with the Ph. Eur. supporting broader use than the other pharmacopoeias.

Device Type	NGI	ACI	MSLI	GTI	Pharmacopoeia
MDI 	Y	Y	Y	Y	Ph. Eur./EMA
	Y	Y	N	N	USP/FDA
	Y	Y	N	Y	ChP
	Y	Y	Y	N	JP
MDI with a Spacer/ Valved Holding Chamber (VHC) 	Y	Y	Y	Y	Ph. Eur./EMA
	Y	Y	N	N	USP/FDA
	Y	Y	N	Y	ChP
	Y	Y	N	N	JP
DPI 	Y	Y	Y	Y	Ph. Eur./EMA
	Y	Y	Y	N	USP/FDA
	Y	Y	N	Y	ChP
	Y	Y	Y	N	JP
Nebuliser 	Y	N	N	N	Ph. Eur./EMA
	Y	N	N	N	USP/FDA
	Y	N	N	N	ChP
	Y	N	N	N	JP
SMI 	Y	Y	N	N	Ph. Eur./EMA
	Y	Y	N	N	USP/FDA
	Y	Y	N	N	ChP
	Y	Y	N	N	JP
Nasal Products 	Y	Y	N	N	Ph. Eur./EMA
	Y	Y	N	N	USP/FDA
	Y	Y	N	N	ChP
	Y	Y	N	N	JP

The world's leading pharmacopoeias differ with respect to use of the MSLI and GTI with the NGI and ACI more broadly and uniformly specified.

Generic submissions, product-specific guidance and product-specific monographs

The FDA has committed to establishing product-specific guidances (PSGs) to support Abbreviated New Drug Application (ANDA) submissions with the goal of stimulating the generic sector and improving access to valued drugs. There are over 2,000 now in place (latest published summary, as of Oct 2024, across all dosage forms) with the number of PSGs for OINDPs increasing steadily[x]. The EMA, in contrast, offers general guidance for generic submissions detailing a stepwise approach as opposed to the FDA's weight of evidence methodology.

For individual products, PSGs are an important reference with respect to impactor choice though most typically indicate methods in USP <601>.

Choosing your impactor: Key takeaways

To summarise, the best impactor for compendial testing for any given OINDP is influenced both by regulatory guidance and practicality. Key points to note are:

- Not all impactors are specified for compendial testing for all types of OINDPs; the exception being the NGI.
- Optimal impactor choice relies on careful consideration of the strengths and limitations of alternative options taking into account product type and formulation chemistry.
- PSGs may point to the use of certain impactors. Product-specific compendial methods may be useful in supporting generic development, even if not ultimately used to provide submission data.
- Amenability to automation, and by extension productivity, can have a major impact on the value of an impactor, over the long-term. Total cost of ownership/operation can be a sensible selection strategy where there is freedom to apply it.

II. Cascade Impaction for Orally Inhaled Products (OIPs)

For OIPs, cascade impaction sizes particles that, because of their aerodynamic size, are likely to deposit in the lung. Such particles are necessarily fine, since coarse particles are unable to penetrate the physiological safeguards in place to protect the lungs. 5 µm is typically taken as the upper limit for deposition in the lungs for the purposes of inhaled drug delivery.

The inherent relevance of cascade impaction for assessing particles of this size range for pulmonary deposition is enhanced by testing under conditions that reflect the mechanism of operation of different products and patient practice. For this reason, compendial test methods differ for each class of OIP.

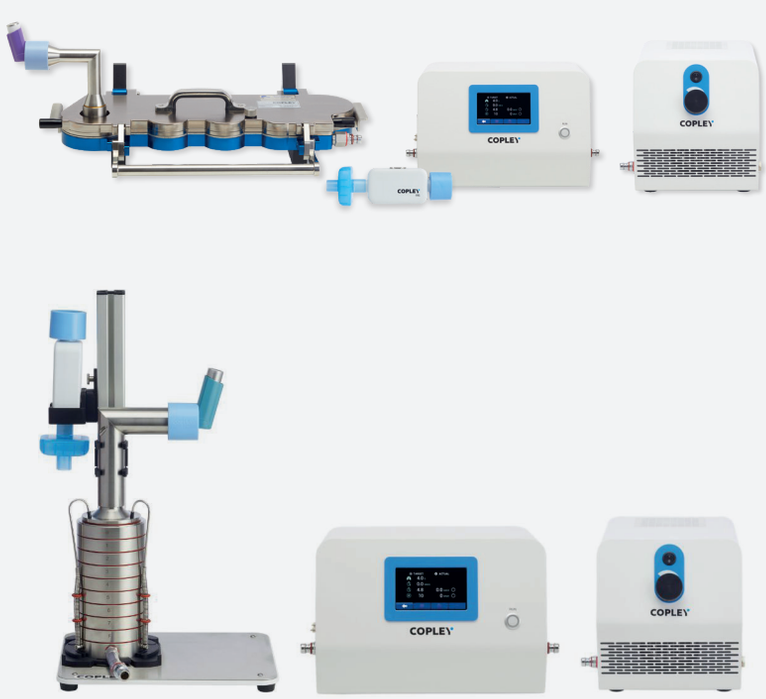
Let's take a closer look at these methods and the rationale behind them.

Metered Dose Inhalers (MDIs)

With an MDI, dose dispersion and drug delivery is driven by an evaporating propellant. The patient is instructed to inhale slowly and steadily as the device is actuated, but the active mechanism of drug delivery means that the inhalation profile of the patient has minimal effect on the characteristics of the dose.

MDIs are therefore uniformly tested at 28.3 L/min, a historical convenience relating to the use of the ACI, or 30 L/min when using the NGI, which was calibrated at 30 L/min for ease.

The figure below shows test set-ups for MDIs which are equally suitable for breath-actuated inhalers (BAIs).



Test set-ups for APSD measurement for MDIs.

Alongside the impactor these set-ups include a(n):

- Vacuum pump to draw air through the system.
- Flow meter to measure air flow rate.
- Induction port to interface device and impactor, typically the standard USP/Ph. Eur. induction port.
- Mouthpiece adapter to provide an airtight seal between device and induction port.
- Breath Actuation Flow Controller, incorporating a timer-controlled solenoid valve, to start and stop air flow, coordinate actuation, and simplify workflow.

MDIs with Spacers/Valved Holding Chambers (VHCs)

The need to coordinate inhalation with device actuation is a hurdle to the effective use of MDIs for certain patients, notably paediatrics and geriatrics; add-on devices are a solution. Spacers and VHCs eliminate the requirement for coordination by acting as a reservoir for the dispersed dose, thereby allowing the patient to inhale the dose by breathing normally. However, the additional volume they insert between device and patient provides an opportunity for particle expansion, impaction, settling and electrostatic deposition. Compendial methods for APSD measurements for MDIs with add-on devices are correspondingly differentiated to assess the impact of these mechanisms; USP Chapter <1602> details requirements [xi].

Example test set-up for APSD measurement for an MDI with spacer.

This chapter specifies APSD measurement in the presence of the add-on device with no delay between actuation and the onset of air flow for the direct comparison of performance with and without the add-on device.

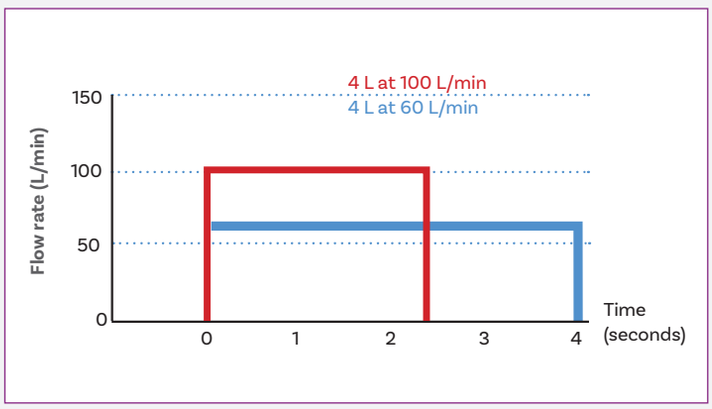
In addition, for VHCs, USP Chapter <1602> specifies a further test to simulate a 'worst case' scenario in which the onset of air flow is delayed for 2 seconds relative to actuation. The aim of this test is to assess actuation into a VHC with a closed valve and an associated delay before administration. Testing with longer delays may also be helpful in elucidating product performance.

The test set-ups shown for MDIs are equally suitable for testing in accordance with these requirements with a Breath Actuation Flow Controller providing the start/stop flow control required to apply a precisely timed delay.

Dry Powder Inhalers (DPIs)

With a DPI, dose dispersion and drug delivery is typically driven solely by the inhalation manoeuvre of the patient, since most devices are passive. The patient is instructed to breathe deeply and or strongly and the pressure drop that they exert across the device when doing so influences the characteristics of the delivered dose.

For DPIs, test flow rates are therefore product-specific with lower resistance devices tested at a higher air flow rate than those with higher resistance, up to a maximum of 100 L/min. A pressure drop of 4 kPa and total inhaled volume of 4L are specified for representative APSD measurement.



Converting these metrics into test parameters involves:

- Measuring the flow rate required to achieve a pressure drop of 4 kPa across the device.
- Determining the time associated with a total test volume of 4L, at that flow rate (see image opposite).

Determining test conditions for a DPI involves determining the air flow rate that gives rise to a pressure drop of 4 kPa across the device and using the resulting figure, in combination with total test volume (4L) to determine test duration.

The result of this process is a test flow rate and duration. The sensitivity of DPIs to test flow rate results in a further stipulation with respect to testing which is to apply 'critical flow' conditions across the device to ensure flow rate stability (see Understanding critical flow.)

The figure below shows test set-ups for DPIs:

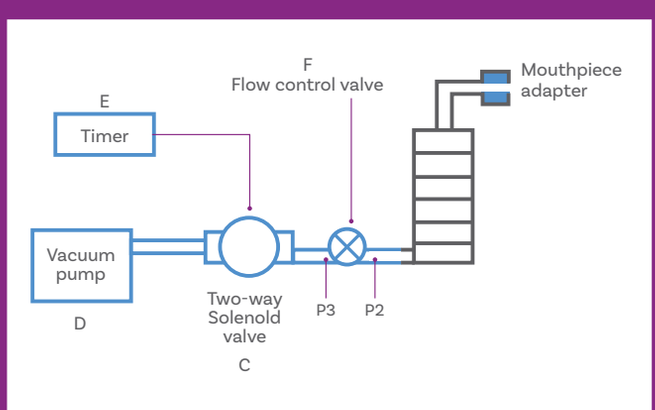
Test set-ups for APSD measurement for DPIs.

The key equipment difference relative to the MDI test set-up is the inclusion of a Critical Flow Controller, in place of the Breath Actuation Flow Controller, to control (and document) all the parameters associated with meeting the critical flow condition. In addition, a more powerful vacuum pump may be needed because of the higher air flow rates required.

Understanding critical flow

In flowing gas systems, the critical flow condition occurs when the pressure downstream of a valve or restriction falls below 50% of the upstream pressure. At this point air flow through the valve reaches sonic velocity resulting in a choking effect; further decreases in downstream pressure have no effect. Under critical flow conditions, flow rate becomes a function of upstream pressure **alone**, rather than pressure drop across the valve.

Within the context of a DPI test set-up (see figure on the right) this means that if P3 is ≤ 0.5 P2 then fluctuations in pressure downstream of the flow control valve will have no impact on flow rate through the device and impactor. This is clearly an excellent outcome with respect to the stability of the test set-up that eliminates downstream pressure variations as a source of variability.

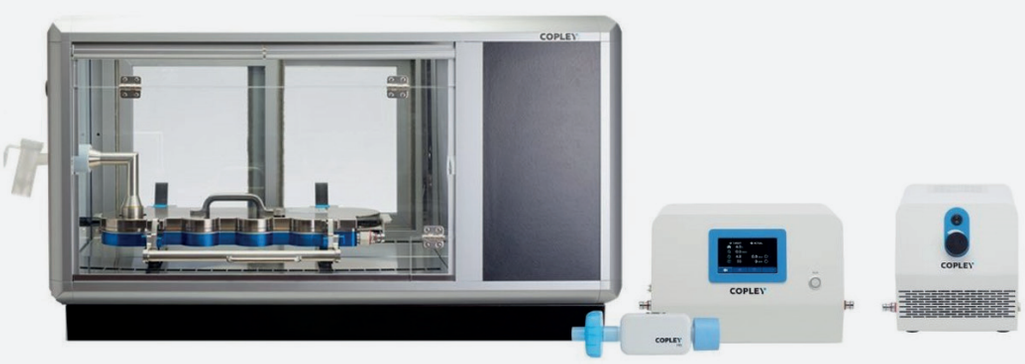


Nebulisers

With a nebuliser, formulation dispersion is an active mechanical process driven by compressed air, ultrasonics or mesh vibration. The patient inhales the resulting mist of droplets by breathing normally through a mask or mouthpiece.

As with MDIs, this active mechanism of drug delivery means that the inhalation profile of the patient has minimal effect on the characteristics of the delivered dose. However, nebulisers are tested at a lower flow rate, at 15 L/min, deemed more representative of the mid-tidal flow rate of a typical adult. Note that compendial methods include no requirement to apply a tidal breathing pattern during APSD measurement, despite the potential for more representative evaluation, because of the additional complexity associated with achieving this condition while simultaneously ensuring a constant flow rate through the impactor.

The figure below shows a test set-up for nebulisers:



A test set-up for APSD measurement for nebulisers.

Relative to set-ups shown for MDIs there are two clear differences:

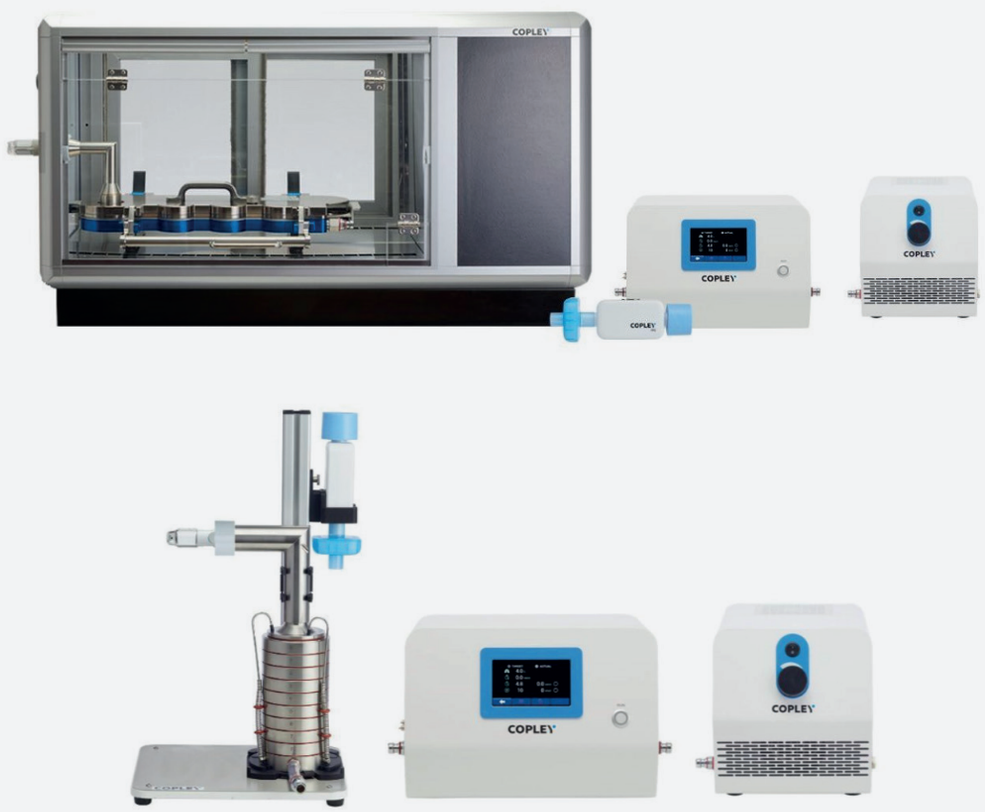
- Only an NGI test set-up is shown, since this is the only impactor with calibrated performance at the required flow rate of 15 L/min.
- The NGI is held in a cooler.

Compendial methods, as detailed in USP Chapter <1601>[xii] and Ph. Eur. Chapter 2.9.44[xiii], specify cooling of the NGI to 5°C when testing nebulisers to reduce solvent evaporation within the impactor. Solvent loss from droplets travelling through the impactor, due to heat absorption from its relatively large metal mass, can skew measured APSDs towards finer values, resulting in unrepresentative measurement. This can be a problem for other types of OIPs but is especially likely with nebulisers hence the compendial specification. Cooling the impactor eliminates the issue and ensures representative and repeatable measurement.

Soft Mist Inhalers (SMIs)

With an SMI, dose dispersion is an active mechanical process, as with a nebuliser, but the patient is instructed to inhale slowly and steadily during use, as with an MDI. Because of the active drug delivery mechanism, the inhalation profile of the patient has minimal effect on the characteristics of the delivered dose and SMIs are therefore uniformly tested at 28.3 L/min or 30 L/min in an analogous way to MDIs.

The figure below shows possible test set-ups for SMIs:



Test set-ups for APSD measurement for SMIs.

These set-ups underline the somewhat hybrid characteristics of SMIs and highlight:

- The potential suitability of both the NGI and ACI for SMI testing, as for MDIs, because of the specified test flow rate.
- The benefits of impactor cooling, as for nebulisers, because of the risk of solvent evaporation, a point emphasised in recent work by the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS)[xiv].

III. Cascade Impaction for Nasal Drug Products

For deposition in the nose, product developers typically target a particle size range of 30 to 120 µm, well beyond the upper sizing limit of cascade impaction. Rather than being used to assess the likelihood of ***targeted*** delivery, for nasal drug products cascade impaction is therefore used to assess the risk of ***off-target*** deposition. By quantifying the amount of drug in the fines of the delivered dose, typically the <10 µm fraction (absolute cut-off value varies between regulators), it quantifies the risk of drug penetrating through the nasal cavity and entering the body via lungs, an unintended and potentially unsafe outcome.

Nasal drug products are broadly classified as sprays, aerosols or powders with multi-dose sprays dominating the market, by volume. Compendial methods for cascade impactor testing reflect commonality between nasal aerosols and nasal powders and their corresponding OIPs, inhalation aerosols (MDIs) and inhalation powders (DPIs), respectively while simultaneously highlighting the lower risk of fines associated with nasal sprays.

Let's take a closer look at test set-ups used for each product type.

Nasal sprays

With a nasal spray, dose dispersion and delivery are achieved by manually actuating a mechanical pump, thereby forcing the formulation through an actuator and orifice. This active delivery mechanism allows for testing at 28.3 L/min or 30 L/min, as with MDIs. However, many widely used nasal spray devices are known not to produce a high level of fines. The instruction to quantify the amount of 'drug in small particles/droplets by cascade impaction', as listed for example in product-specific guidance for fluticasone propionate[xv] (metered, spray; nasal) may therefore be met by simply determining the amount of drug in the **entire** sub-ten microns fraction, rather than via full resolution APSD measurement.

The figure below shows a complete, full resolution cascade impactor test set-up for nasal sprays (NGI) and alongside a Fast Screening Impactor (FSI), an abbreviated stack based on the NGI preseparator.

Examples of automated test set-ups for APSD measurement for nasal sprays: full resolution (left) and abbreviated stack (right).

Several features of these set-ups merit further discussion.

Firstly, the test set-ups feature an automated shake, fire and flow control platform (Vertus®). For delivered dose uniformity (DDU) testing for nasal sprays, USP <601> recommends the use of a 'mechanical means of actuating the metering system or pump assembly to deliver doses for collection'[viii]. This practice eliminates the potential for variability from actuation technique and is therefore similarly relevant for cascade impactor testing. The automation platform allows the analyst to ensure highly consistent operation of the product by setting key parameters such as shaking speed, angle, and duration; the magnitude of any delay between shaking and firing; actuation force profile; and storage orientation during testing.

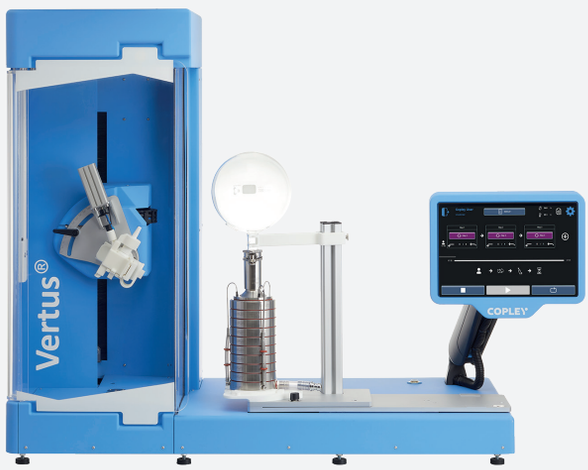
Secondly, both images show a glass expansion chamber into which the device is actuated. This allows atomisation and dispersion of the dose prior to sampling with expansion chambers of 2 L and 5 L volumes typically the preference for nasal sprays. The goal is to optimise the method towards a 'worst-case' scenario with respect to pulmonary deposition, by selecting an expansion chamber that maximises atomisation of the emitted dose entering the impactor.

Finally, focusing on measurement with the FSI, this produces two fractions, with a range of inserts enabling a 5.0 µm cut-off point across a flow rate range of 30 – 100 L/min. A detailed discussion of abbreviated impactors lies beyond the scope of this ebook but since these fractions can be associated with deposition in the upper respiratory tract or the lung. The FSI clearly offers potential for the efficient assessment of nasal sprays with respect to off-target delivery, especially in combination with an automated actuation platform for high productivity testing.

Nasal aerosols

With a nasal aerosol, dose dispersion and delivery are driven by evaporation of a propellant upon manual actuation. This energetic process is prone to producing high levels of fines, relative to nasal sprays, hence the compendial specification for full resolution APSD measurement, using the same method specified for inhalation aerosols (MDIs)[viii].

The figure below shows a test set-up for nasal aerosols.



An example test set-up for nasal aerosols.

This set-up is identical to the one shown earlier for nasal sprays. Though there is no compendial recommendation for mechanical actuation for nasal aerosols the adoption of automated shake, fire and flow control platforms can help to improve data consistency and reduce analyst time/effort (see section IV, Automation). A 1 L glass expansion chamber is typically sufficient for full development of the aerosolised cloud for nasal aerosols.

Nasal powders

Currently, the number of commercialised nasal powders is relatively few with operating mechanisms varying from device-to-device. That said, dose release and dispersion is typically passive, driven solely by the patient applying some kind of inhalation manoeuvre. Compendial specifications for testing are consequently strictly analogous to those for inhalation powders (DPIs).

The test set-ups for nasal powders are identical to those for DPIs (see earlier) with no requirement for a glass expansion chamber. A preseparator is only required for carrier-based formulations.

IV. Establishing Good Practice

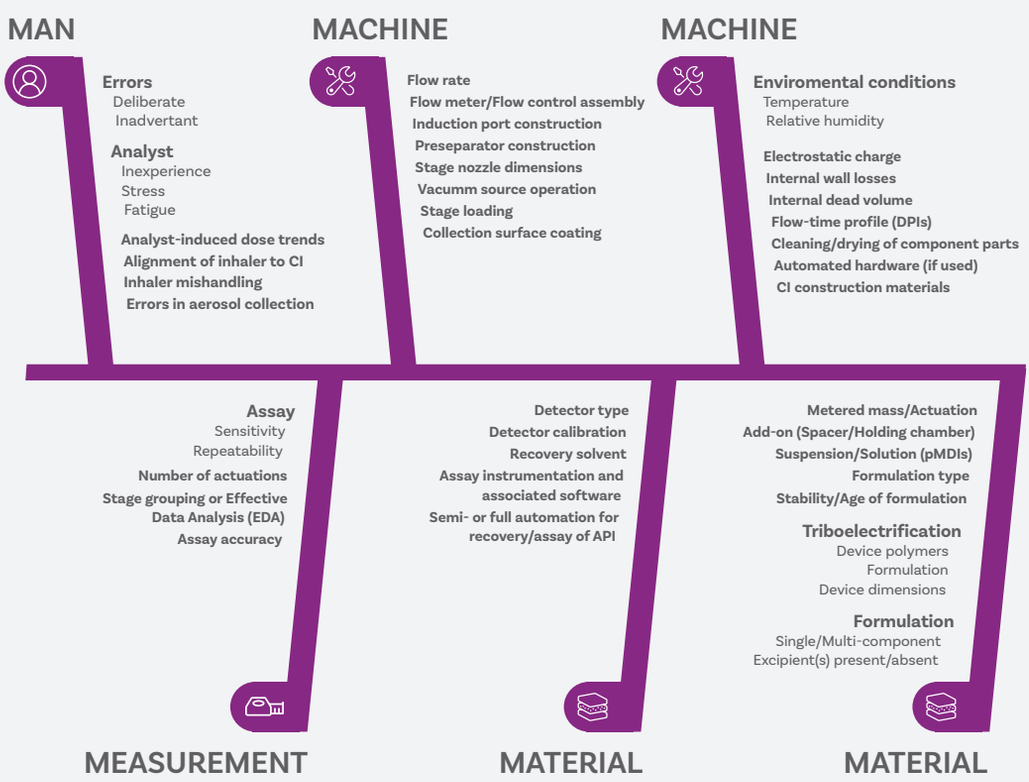
An array of factors, from the global to the local, complicates the effective routine application of cascade impaction for OINDP characterisation. Such factors include:

- Relatively rapid expansion and geographic diversification of the OINDP community which means that detailed knowledge and expertise can be somewhat thinly spread; often there is a shortage of skilled analysts to meet growing workloads.
- The ongoing evolution of compendial methods and the regulatory framework.
- Test set-ups are specific to individual products with no two products typically tested in precisely the same way.
- Each individual analysis is a multistep, largely manual process that generates substantial amounts of data; rigorous training is required to ensure consistency from start to finish.

Against this backdrop, pragmatic advice on good practice and the minimisation of variability is extremely helpful.

An overview of sources of variability

The fishbone diagram below was developed by a working group of IPAC-RS to summarise sources of variability in cascade impactor testing [xvi]. It's an invaluable reference for method development and establishing good operational practice that safeguards data quality. Reducing variability cuts the risk of an erroneous out-of-specification result and more generally makes measurement more reliably differentiating.



A fishbone diagram showing the multiple sources of variability associated with cascade impaction.

Sources of variability are typically grouped under four headings:

MAN – variability associated with operator practice.

MEASUREMENT – variability associated with the method.

MACHINE – variability associated with the test set-up and equipment used.

MATERIAL – variability associated with the specific product and its use.

Looking across these factors we can draw out illustrative examples of the many questions faced during method development and routine deployment of the technique, such as:

- How many device actuations are needed to avoid stage loading issues while at the same time allowing accurate assay, for every fraction, for each active?
- Is the product stable? What actuation conditions are required to ensure representative dose delivery?
- What collection surface coating is required to minimise particle bounce? And how can we ensure consistent application?
- How quickly does air flow rate though the DPI ramp up to the target value? Are we applying a consistent flow time profile?
- Which is the best solvent to use for drug recovery, for this product?
- Are stage nozzle dimensions still in specification given that there are signs of corrosion?
- Is the flow meter reading accurately? When was it last calibrated?
- How can we maintain analyst motivation and focus to minimise inadvertent errors?

This far from exhaustive list illustrates the multi-faceted nature of minimising variability in cascade impaction measurements to maximise the integrity and value of the resulting data.

Let's take a closer look at some areas where there are established solutions and good practice to adopt.

Flow control

As we've discussed, the velocity at which particles travel in a cascade impactor influences where they will collect. Air flow rate defines that velocity and by extension the size fractionation characteristics of the impactor. Stokes Law describes the relationship between stage cut-off diameter (D_{50}) and air flow rate (Q) and is useful in clarifying why effective flow control is so important:

$$D_{50,2}/D_{50,1} = (Q_1/Q_2)^{1/2}$$

[Where D_{50} is stage cut-off diameter and Q is volumetric air flow rate]

The general compendial specification for OIP testing is that test flow should lie within +/-5% of the target flow[viii,ix]. Note, this is a 'composite' accuracy including all errors from setting, determining, and controlling flow rather than simply flow meter accuracy. Using Stokes Law, we can determine that a +/-5% change in flow rate equates to +/-2.5% variability in stage cut off diameter. **Intra-analysis** variability in test flow rate erodes the 'sharpness' of stage cut off values while **inter-analysis** variability impacts measurement repeatability and reproducibility.

However, we also know that air flow rate can influence the performance of OIPs, notably DPIs. This is an important, additional motivation for precise flow control.

It is for these reasons that flow meters are an essential element of every cascade impactor test set-up – as we've seen – along with additional **flow control** ancillaries, for certain products. For optimal flow meter use and robust control in cascade impaction measurements bear in mind the following points:

- The compendial requirement is to calibrate air flow at the **exit** of the flowmeter, the inlet to the impactor. Common practice is rather to calibrate flow meters for **inlet** flow, but it is possible to mathematically correct for this if necessary[viii].
- Variations in temperature and atmospheric pressure, relative to calibration conditions, can distort flow meter readings. Mathematically correcting for this is also vital.
- Values measured using a **mass** flow meter will require conversion to **volumetric** flow rates. More sophisticated flow meters will do this automatically which is helpful.

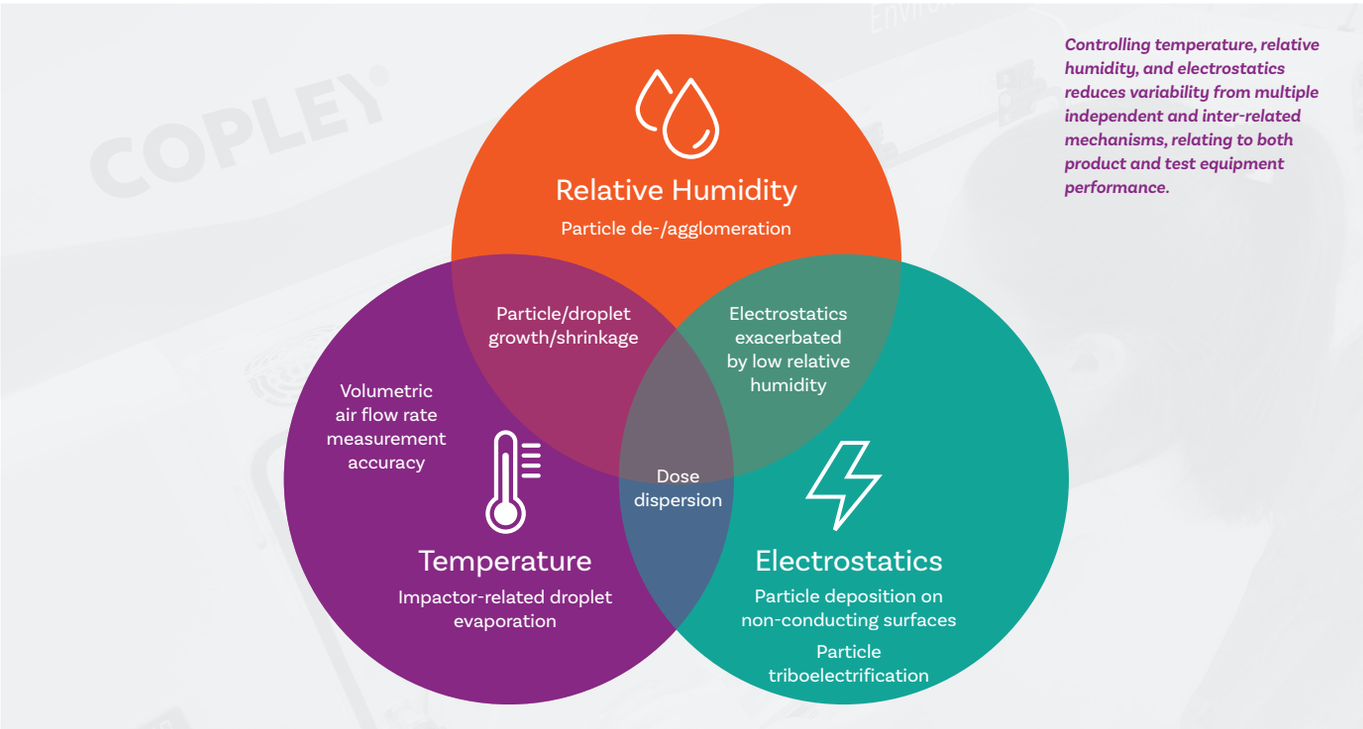
Beyond the flow meter, achieving precise flow control also relies on careful consideration of the size of connecting tubing and effective leak testing[xvii]. Larger bore tubing is preferable, within the constraints of other system requirements, to reduce pressure drop. For the NGI, the user guide recommendation for leak testing is for a rise rate of <100 Pa/s at a vacuum of 2.5 kPa which equates to a leak rate of <0.5% of total flow at the lowest calibrated flow rate (15 L/min).

Lastly, when it comes to minimising the influence of flow rate on APSD data, the ability to input actual rather than target test flow rate into data analysis software can be helpful.

Environmental control

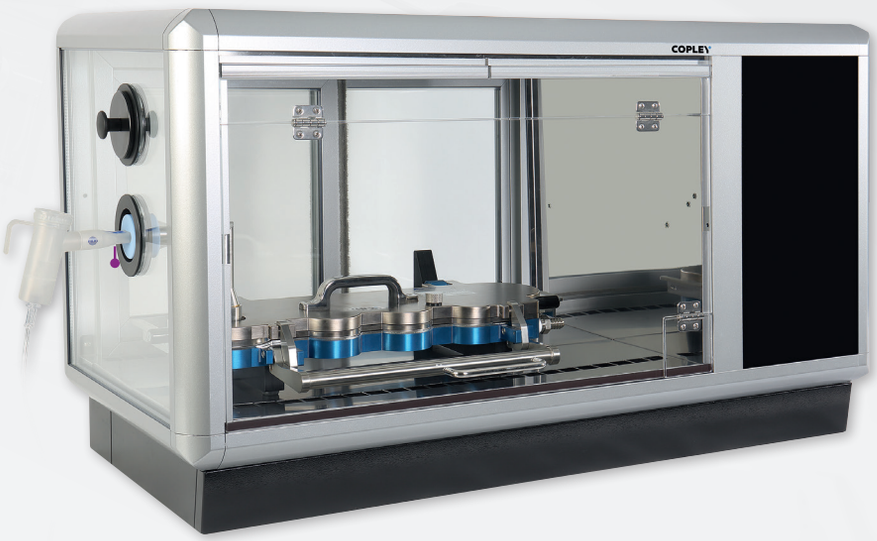
Environmental conditions – temperature and relative humidity - are identified as a source of variability for the impactor (MACHINE) and may also impact the performance of the product; triboelectrification is highlighted as a source of variability for the product (MATERIAL).

If we group the control of temperature, relative humidity and electrostatics in the test environment together, under the umbrella term environment control, then we can see that robust control has the potential to minimise variability via a number of mechanisms.



Controlling temperature, relative humidity, and electrostatics reduces variability from multiple independent and inter-related mechanisms, relating to both product and test equipment performance.

From a product perspective, susceptibility to the test environment arises because drug delivery is a dynamic process, influenced by the conditions under which it occurs. High relative humidity can encourage powder particles to agglomerate, for example, while the rate and extent of droplet growth or shrinkage can be influenced by temperature. Turning to the performance of test equipment, variations in temperature can impact the accuracy of air flow rate measurements, while electrostatic effects can impact particle deposition behaviour, notably on non-conducting parts of the test set-up; low relative humidity can exacerbate such effects because of the high conductivity, and by extension 'earthing' effect of any water present.



The NGI Cooler™ and EnviroMate™ benchtop environmental chamber are complementary, dedicated solutions for controlling the OINDP test environment.

Solutions for controlling temperature and relative humidity range from complete laboratory climate control, through lab-wide air conditioning systems, to dedicated workstations that accommodate the equipment required for testing. In the figure above the upper image shows the **NGI Cooler™**, which efficiently meets the requirement to test nebulisers at 5°C (see nebuliser test set-up). Below is **EnviroMate™** a larger, benchtop environmental chamber that comfortably accommodates all the equipment required for cascade impactor testing for all types of OINDPs, controls temperature across the range 17 to 35°C +/- 2°C, relative humidity across the range 15 – 85% to +/-5% and incorporates electrostatic mitigation devices.

Additional effective strategies for mitigating the effects of electrostatics include[xviii,xix]:

- Grounding of equipment and operators; antistatic wristbands are frequently used to minimise charge accumulation.
- Restricting the use of gloves and/or specifying the types of gloves that may be worn.
- Careful choice of protective lab equipment - anti-static shoes, clothing and/or mats are all commonplace.
- The use of electrostatic eliminators and guns, and ionisation bars.

Automation

While the product-specific nature of cascade impaction test set-ups make the technique poorly amenable to end-to-end automation, many repetitive tasks are common to multiple measurements. Examples range from consistent shaking, priming and actuation of the product, to collection surface coating, and the dispensation and agitation of precisely metered volumes of solvent in drug recovery.

Investing in solutions to automate such steps can reduce analyst fatigue and the risk of repetitive strain injury, thereby making a substantial difference to productivity. At the same time automation ensures strictly consistent practice, eliminating operator-to-operator variability.

Off-the-shelf solutions are the most accessible option for anyone beginning the process of automation. Customised solutions are the alternative, but costs and risk are higher than with a proven, validated system. Off-the-shelf solutions offer demonstrable reliability and should be minimally demanding with respect to cleaning, maintenance and training. For MDIs and nasal drug products, device actuation or firing is more commonly automated, but more generally, for all products, it is aspects of the manually intensive, step-by-step drug recovery process that are prime candidates for automation.

Automating just a simple step, such as induction port rinsing, is an excellent way to begin the process of semi-automation. It allows analysts to assess the benefits, to generate some confidence in what might be achievable and to gather data to justify more complex projects. Furthermore, since off-the-shelf solutions require only relatively modest investment and are transferable between products, use can begin in R&D and then proceed step-by-step with the product towards commercialisation. Installing identical systems in parallel is an easy way to scale-up but solutions from the same ‘family’ may also allow for streamlined method transfer facilitating progressively more complex and extensive automation as analytical requirements ramp up.

Quantifying the benefits of semi-automation

The results below are from back-to-back cascade impaction measurements for a Salbutamol Sulphate CFC-free MDI (100 µg, IVAX Pharmaceuticals, Ireland) carried out by two analysts at Presspart Manufacturing Ltd (Blackburn, UK), with manual and automated device actuation (**Vertus® II** for dose collection, **DecaVertus®** for firing to waste)[xx]. Measurements were made at the beginning and end of product life in triplicate, using an NGI.

Details	MB (In %)	% RSD of MB	ISM in mcg	% RSD of ISM
Between 2 analysts with automated shake and fire system	88.91	8.2	54.01	9.2
Between 2 analysts with manual actuation	85.42	9.3	45.08	12.5

Summarised cascade impaction test data measured by two analysts, manually and using an automated shake, fire and flow control platform (Where MB is mass balance, ISM is Impactor Sized Mass and %RSD is % Relative Standard Deviation).

The combined automated cascade impaction data for both analysts (24 readings) show less variability than the equivalent manual data; %RSD for the MB is 8.2 rather than 9.3 and % RSD for the ISM is reduced to 9.2 from 12.5. This is a clear gain in terms of data quality.

At the same time, automated testing took around **30% less time** than manual, a significant productivity gain; training requirements were simultaneously reduced.

Stage mensuration

At the beginning of this ebook we highlighted the role of well-defined specifications and better manufacturing practice in producing cascade impactors that were fit-for-purpose for OINDP testing. Today, we can purchase cascade impactors built and inspected to the most exacting standards, but dimensions can change with use, a key issue being the corrosion, erosion and occlusion of nozzles.

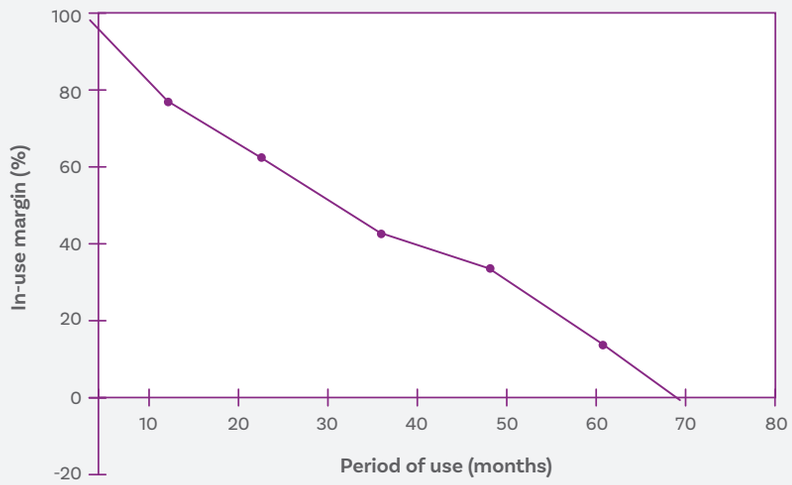
Stage mensuration is the physical process of measuring the critical dimensions of a cascade impactor to ensure consistent aerodynamic performance within well-defined limits. In practice, it involves measuring every nozzle, of every stage and may also include checks of the dimensions of, for example, hinges and cups. For those new to cascade impaction this reliance on stage mensuration, as opposed to routine calibration with a standard, may seem surprising but it is, in fact, the simplest and most effective option.

Compendial methods specify the need for stage mensuration 'on a regular basis' leaving the question of frequency open to judgement and justification. Annual mensuration tends to be the minimum, but a higher frequency may be needed depending on formulation chemistry and impactor compatibility. Typically stage mensuration is outsourced because of the expensive automated vision systems required for precise, highly reproducible measurement of nozzle diameters that are fractions of a mm in size.

A stage mensuration certificate quantifies current cascade impactor performance via two parameters: Effective Mean Diameter (EMD) and In-Use Margin. Understanding the significance of these parameters is the key to interpreting and using stage mensuration data.

- ***Effective Mean Diameter (EMD)*** – Theoretical analysis shows that a multi-nozzle cascade impactor stage behaves as if all nozzles are equal in size to an EMD and that changes in EMD can be securely correlated with changes in stage cut-off diameter [xxi]. EMD values therefore reveal the stage cut-off diameters associated with the current state of the impactor.
- ***In-Use Margin*** – Comparing EMD values with nominal specifications for an individual stage quantifies the extent to which the impactor remains within the defined manufacturing tolerances – the In Use Margin. For example, if stage mensuration values for Stage 7 of an NGI indicate an EMD of 0.206 mm then the In-Use Margin is 100%, since this is the nominal value for the stage. Conversely, an EMD of 0.196 mm reduces In-Use Margin to 0% since the manufacturing tolerance is +/-0.01 mm. The impactor is on the edge of becoming unfit for further use.

Tracking In-Use Margin over subsequent stage mensurations is a good way to determine the required frequency of stage mensuration, and crucially, to identify when the impactor will require remedial attention.



A plot of In-Use Margin as a function of time predicts a date for remedial attention and provides evidence for the justification of stage mensuration frequency.

If stage mensuration data indicate that the nozzles have become too large, then stage replacement is the only option. Usually, however, the opposite trend is observed since corrosion often results in the deposition of oxidised impurities and nozzle occlusion. Where this has occurred then either rigorous cleaning or stage pinning may restore performance.

Understanding the significance of accurate stage mensuration

Consider Stage 7 of an NGI which has nozzles with a diameter of 0.206 mm +/- 0.01 mm (10 µm); a diameter anywhere from 0.196 to 0.216 mm lies within the manufacturing tolerance.

The quoted optical reproducibility of the advanced optical system we use for stage mensuration is 1 µm which means that in the worst-case measuring system errors are, at most, 5% of the manufacturing tolerance range.

Contrast this, with the situation with a less accurate system; reproducibility can easily be as much as +/-5 µm, five times as high. Now, measurement errors are effectively 'using up' as much as 25% of the manufacturing tolerance thereby taking the impactor out of the margin for acceptable use, earlier. Furthermore, if reproducibility is not properly accounted for then there is a substantially increased risk of using an out-of-spec impactor.

The benefits of accurate and reliable stage mensuration are both significant and valuable.

V. Summary

We hope this ebook has helped you to understand the fundamentals of cascade impaction, to appreciate its value and how best to use it. Most importantly we hope you:

- Keep the principles of cascade impaction in mind when using the technique, to develop robust methods and ensure good operational practice.
- Recognise that every cascade impaction method may be necessarily unique, but core know-how is universally relevant.
- Realise that a cascade impactor may not be a model of the lung but it is the most tried and trusted in vitro tool available for relevantly characterising the size of OINDP aerosols.

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Notes

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