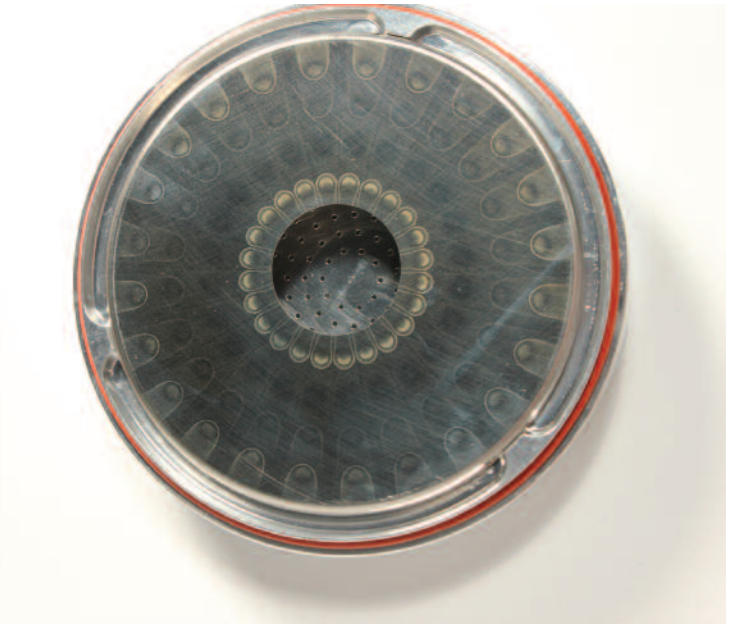
# Calibrating cascade impactors with particles—Approaches and pitfalls

***Get the most value by defining the scope in advance and making sure all particles are one size for each data point***



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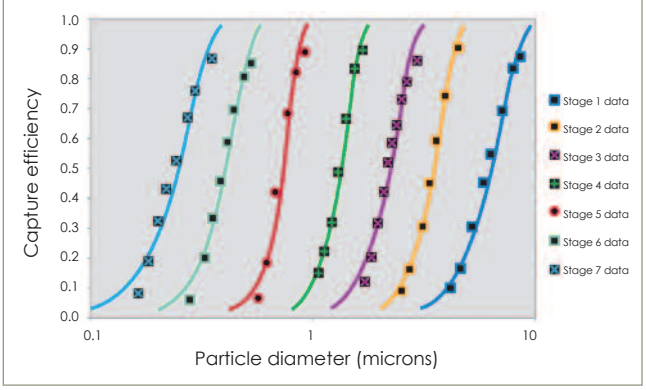
Accurate quantification of the performance of a cascade impactor requires calibration with particles. The scope of the work needed, the methods and the pitfalls of a calibration with particles are all important considerations. Indeed, the word "calibration" itself is often misused in the literature of the inhaler testing community to mean the optical inspection of the stage nozzles. The following article explains the typical goals of a calibration, describes the methods for accomplishing these goals and explain some of the things that can go wrong or be misunderstood if certain aspects of the method are not maintained. Overall, the goal is that the inhaler testing community develops a greater appreciation for the meaning of and value of "calibration with particles" and a greater sense of confidence in the ability of modern methods to deliver a high quality, and quantitative, statement of the performance of cascade impactors.

## Fate of particles in a cascade impactor

Cascade impactors separate a polydisperse aerosol into groups according to the size of the particles, technically the aerodynamic diameter of the particles. The mass of material captured on any given stage of the impactor, which is the measured outcome of an inhaler test, depends on the size distribution of particles entering the impactor and the efficiency with which particles are captured by the given stage *and* by all stages preceding the given stage.[1] The goal of a comprehensive calibration of an impactor with particles is to quantify the capture efficiency curve for particles on each stage, such as the curves shown in Figure 1 for the stages of the NGI operating at 100 L/min. In some cases, the calibration with particles may have a more lim-

**Figure 1**

**Calibration data and stage efficiency curves for the NGI, 100 L/min[2]**



ited objective, such as determining solely the particle size that is captured with 50% efficiency (D50) for one or more stages of the impactor.

To create this kind of data, it is important to be able to pass particles of a single size into the impactor, to quantify the amount captured and to interpret the data in such a way as to deduce meaningful information for the inhaler tester, who is seeking to characterize one or more inhaler products. Some surfaces of an impactor are intentionally meant to capture particles while other surfaces in the impactor do so despite the best intentions of the designer. Therefore, it is important that the calibration method minimize the effects of unintentional behavior on the data quality and interpretation.

Finally, we note that optical measurement of the nozzles of a cascade impactor is *not* calibration of the impactor. Of course, before calibrating with particles, it is critical to measure the nozzles quantitatively. In that way, subsequent optical examinations after some period of use will reveal whether the impactor will perform sufficiently close to the calibrated stage efficiency curves. This subject has been covered adequately elsewhere.[2,3]

## Generating a particle of a known size

To calibrate an impactor with particles, the first and fundamentally challenging question is "how best" to deliver a particle of a known size to an impactor.

Chen, et al.[4] review many methods of generating particles for calibration purposes. However, the one and only method of generating a stream of round particles, all with a specific diameter, is the principle of the vibrating orifice aerosol generator (VOAG).[5] (See also www.tsi.com/vibrating-orifice-aerosol-generator-3450/.) This device pushes liquid at a known and constant rate through a small orifice, one that is piezoelectrically vibrated to produce a regular instability in the liquid jet. The jet then breaks into precisely-equal volumes of liquid that then quickly take on a round shape due to surface tension. Each volume of liquid is known, simply from the liquid delivery rate divided by the frequency of vibration, and therefore the size of the droplets is precisely known.

Even with this reliable mechanism, approximately 5% of the droplets each manage to coalesce with other droplets near the point of creation of the individual droplets, producing so-called "doublets."[6] Therefore, when calibrating an impactor, it is necessary to remove these doublets, most conveniently accomplished with a small impactor.[7] The absence of the doublets after the removal step can be confirmed with a time-of-flight particle sizer (e.g. the TSI Aerodynamic Particle Sizer, TSI Incorporated, Shoreview, MN, US). With this method, a steady stream of particles of a precisely known size can be delivered to a cascade impactor.

One other advantage of this generation method is that the resulting particles are liquids. Therefore, there is no concern about bouncing from the impactor surface. So that the liquids maintain their size on their path to the impactor, it is important that no evaporation occur. Finally, it is convenient if the liquid contains a material that is easily detected so that the amount captured on the impactor surface is readily quantified. Trace uranine in oleic acid is one of the best liquid solutions for this purpose because the oleic acid is non-volatile and the uranine has a strong fluorescent absorption detectable by inexpensive fluorometers.

Marple, et al. employed the oleic acid/uranine/VOAG method in the calibration of the NGI.[8] For this reason, and because the stages of the NGI were chosen to be close to the nominal design of the NGI, these calibration results are known anecdotally as the "archival" calibration of the NGI. The NGI is the only impactor in the pharmacopeial handbooks calibrated with particles using this state-of-the-art method.

In considering sound methods of generating particles of a known size for calibration of an impactor, it is impossible to have a "standard MDI" or "standard DPI" with which to calibrate an impactor. Such devices would merely produce polydisperse aerosols made of particles of an unknown size. No matter how repeatable may be the mass collected on each stage of the impactor into which one discharged such a device, the size of the aerosol particles would simply not be known.

## After the particles go into the impactor, what occurs?

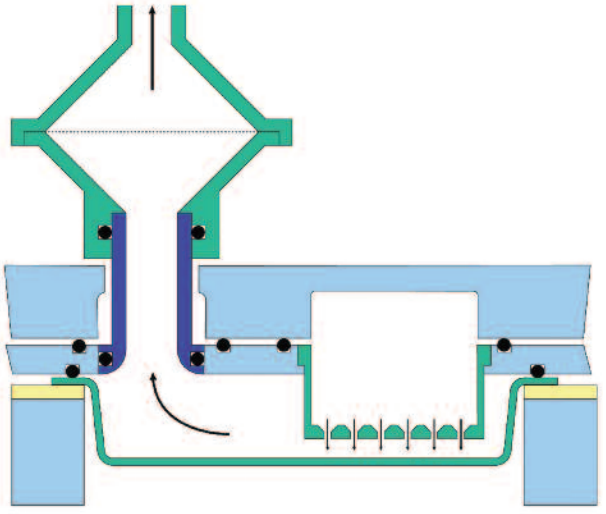
Assuming we have successfully crossed the hurdle of creating a steady stream of particles of a precisely known size, the next subtlety of calibrating with particles is the seemingly simple question: How much particle mass is delivered to a given stage of the impactor? This question is important because to calculate the efficiency with which the given impactor stage captures particles of the given size, one has to know the mass of particles captured by the stage *and* the mass of particles delivered to the stage. Problematically, we may generally know the mass rate of delivery of particles to the inlet of the impactor, but we do not know how much particle mass is removed by upstream

impactor stages or by wall losses in any tubing or interstage passageways. Essentially, despite possibly our best control of the generation rate of particles, we do not actually know the mass rate of delivery of particles to a given stage.

For this reason, the only way to know the mass of particles going into a given impactor stage is to add all of the intentionally deposited, unintentionally deposited and airborne particles *downstream* of the nozzles of the impactor stage being calibrated. Figure 2 shows schematically, for the calibration of the NGI, the way in which a filter holder was inserted into the flow stream to remove and capture the airborne particles downstream of the stage being calibrated. By washing the walls of the interstage passageway to this filter (which quantifies the "wall losses"), quantifying the mass of particles captured on the filter and washing the intentionally deposited material in the impactor stage cup, the efficiency of the stage for the given particle size being tested could be calculated (fractional efficiency equals intentional deposits divided by all deposits and the filter catch).

**Figure 2**

**Schematic diagram of the air flow path and downstream filter for calibrating one stage of the NGI**



## What occurs if unintentional large particles are allowed into the impactor?

Unintentional doublets, created partially by the VOAG method, have a diameter that is 1.26 times the size of the intentional singlet particles (1.26 is the cube root of 2). The measured efficiency at a given particle size, $E_m(D)$, is related to the efficiency of capturing singlet particles, $E_s(D)$, by the following expression:

$$E_m(D) = 0.95E_s(D) + 0.05E_s(1.26D) \quad (1)$$

Here, the figures 0.95 and 0.05 derive from the estimate that 5% of the particle mass forms into doublets.[6] We can estimate the effect of allowing doublets into the impactor during a calibration by considering the typical "S" shape of a stage efficiency curve, which can be represented with cumulative log-normal or hyperbolic tangent functions.[2] First, there is little effect on the estimated value of the "cut-point" or D50. The qualitative reason for this insignificance of the doublets on the estimated D50 value is that the stage efficiency curve has a steep slope in the region of D50. Although doublets may be captured much more efficiently than singlets, the singlet diameter generated to create the 50% measured capture efficiency value is only slightly smaller than the true D50 value of the singlets.

However, introducing doublets into the impactor during the calibration increases the perception that the impactor stage reaches 100% efficiency, when in practice it may not actually be achieving this efficiency. Failure to reach 100% stage efficiency increases the propensity of an impactor stage to exhibit wall losses or particle bounce. For example, in our laboratory, with the VOAG and no doublets, we have observed the inability of stages 1 and 2 of the Andersen impactor to reach 100% capture efficiency (Figure 3), in contrast to the stage efficiency curves reported by Vaughn.[9] In our own work on the calibration of the Andersen impactor, with no doublets entering the impactor, the measured stage efficiency curves actually decrease when the particles become larger than approximately two times the D50 value. We note, however, that the D50 values themselves agree well with those stated in the pharmacopeia (5.8 microns for stage 1 and 4.7 microns for stage 2; 28.3 L/min flow rate).

## What occurs if particles entering the impactor are not all the same size?

Various nebulizers and atomizers are available for creating droplets. Therefore, it is possible to disperse standard, nearly-uniform particles into a nebulizer or atomizer, and to suspend them in an air stream and pass this aerosol into an impactor for calibration purposes. These methods tend to produce log-normal particle droplet distributions. Upon drying, the native uniform particles remain, with a geometric standard deviation of approximately 1.1 to 1.2. When such particles approach an impactor stage, the particles larger than the mean diameter are captured more efficiently than the mean, and the particles smaller than the mean diameter are captured less efficiently than the

mean. These qualitative tendencies do not offset each other. Rather, a log-normal polydisperse incoming aerosol with a mean diameter smaller than the actual D50 value of the stage is captured with a greater efficiency than if all the particles were exactly the mean diameter. Conversely, a polydisperse incoming aerosol with a mean diameter larger than the actual D50 is captured less efficiently than if all the particles were exactly the mean diameter. Surprisingly, within reasonable values of the geometric standard deviation, the measurement of the D50 itself is not affected by the polydispersity of the incoming aerosol. (See references 1 and 2 for the mathematics behind these remarks; see also reference 10 for a polydisperse aerosol test that employs this principle).[1,2,10]

The meaning of this observation is that calibrations with polydisperse aerosols tend to make the stage efficiency curves look "flatter," or less sharp, than if calibration particles were all the same size. The impactor, therefore, appears to have more stage overlap than it actually does, making the impactor appear to perform worse than it actually does.

In principle, contaminants in the nebulizing or atomizing solution will add to the native standard particle or form fresh residue particles. These contaminants can be important when making particles smaller than approximately 50 nm, but such particles are well below the size of particles of interest to the inhaler testing community.

## A scope of work to fit the objectives—How many particle sizes are sufficient?

The key quantity one aims to determine from a calibration with particles is the particle size that is captured with 50% efficiency (D50; sometimes called the "cut point"). The second-most important determination is the degree of overlap from one stage to another, a feature that relates to the "sharpness" of the stage efficiency curve and how near the D50 values are to each other from stage to stage of the impactor.

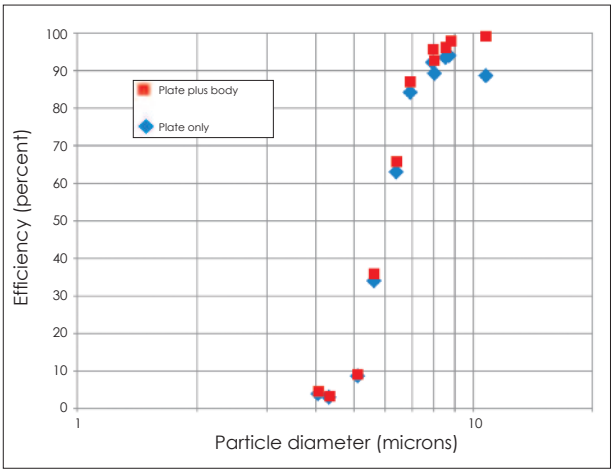
To determine D50 with the least amount of laboratory work, one needs to generate two particle sizes: one in which the particles are captured with an efficiency just smaller than 50% (e.g. in the range of 40% to 50%) and one in which the particles are captured with an efficiency that is just larger than 50% (e.g. 50% to 60%). It is almost impossible, other than by serendipity, to generate a particle size that is captured with 50% efficiency. Usually, although one may try, one misses the 50% efficiency point, makes an adjustment to a slightly different particle size and misses the 50% efficiency point again—but ideally just on the other side of 50% from the first point. Even the most skilled and experienced calibration scientists struggle with "dialing in" the 50% efficiency point.

With two points close to the 50% efficiency point, one then must assume a shape to the stage efficiency curve (linear, log-normal, or hyperbolic tangent) and compute the D50 value. Christopher, et al.[11] have shown that for much of the calibration data available in the open literature, there is no meaningful difference in the calculated D50, whether one assumes a linear or a log-normal shape to the stage efficiency curve.

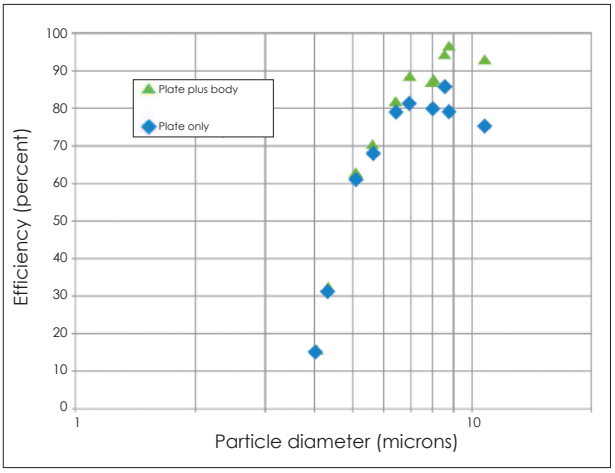
One of the worst problems for impactors is "tailing," meaning that the stage efficiency curve never reaches zero nor 100%. Consequently, the next-most important data to acquire are the size of parti-

**Figure 3**

**Calibration of Andersen stages 1 and 2 at 28.3 L/min**




Stage 1

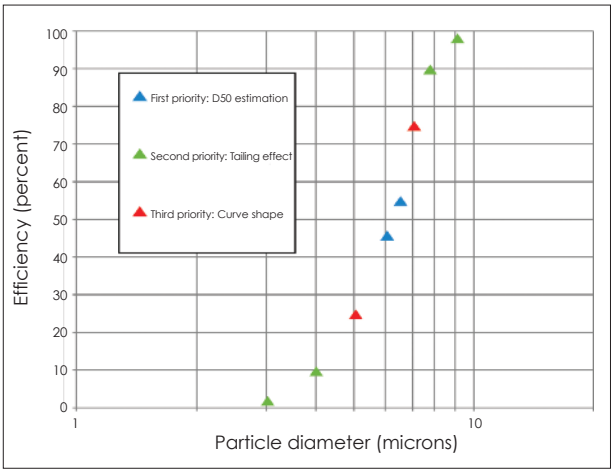



Stage 2

cles captured with 2%, 10%, 90% and 98% efficiency. Finally, to complete the stage efficiency curve, and thereby have the ability to assert the capture efficiency for any size particle, one should aim for particles captured with 25% and 75% efficiency. We depict this strategy in Figure 4, where the blue dots are the first two data points that allow the calculation of D50, the green dots are the second set of data points that ensure the absence of "tailing" of the stage efficiency curve and the red dots are the last two data points that permit the completion of an accurate stage efficiency curve.

**Figure 4**

**Strategy for balancing laboratory workload versus calibration objectives**




## Calibration at unsteady flow rates

In the testing of dry powder inhalers, the device is attached to the inlet of the impactor when there is no flow going into the impactor. The flow into and through the impactor is then started, maintained for a short time (typically four seconds), then shut off. This flow profile is thought to simulate the way that a patient uses a dry powder inhaler much better than does a steady flow through the device. However, this transient flow profile introduces uncertainty to the impactor data interpretation because the stage efficiency curves and the D50 values are changing with time during the startup and shutdown.[12]

We are not aware of any attempts to calibrate an impactor with particles at an unsteady flow condition. However, Mohammed, et al.[13] have examined the behavior of the Andersen impactor and the NGI at unsteady flow conditions from the aspect of decreasingly smaller sample volumes. A clearer understanding of these and related DPI results would likely result from a purposeful calibration of the impactors at unsteady-state flow conditions.

## Summary

Calibrating an impactor with particles, using state-of-the-art methods, enables the user to have full confidence in the size fractionation behavior of the impactor. The VOAG method with a doublet-removing impactor, remains the gold standard for generating particles of a precisely known size, thereby yielding the most authentic and defensible data.

Of the various decisions one must make when approaching an impactor calibration with particles, the following items must be addressed:

1. Polydisperse aerosols tend to over-emphasize the overlap between stages, inaccurately making impactor performance appear worse;

2. The doublets and triplets of the VOAG method, or any such related method, if not removed from the aerosol stream, erroneously increase particle capture efficiency and can mask inadequacies in the capture efficiency for large particles on a given stage;

3. One data point between 40% and 50% efficiency and one data point between 50% and 60% efficiency must be obtained for a good estimate of the D50 value, no matter how many other data points one may determine;

4. It is best to obtain one point at 2%, 10%, 25%, 45%, 55%, 75%, 90% and 98% capture efficiency to establish the complete stage efficiency curve;

5. Optical inspection of the nozzles is necessary for a meaningful calibration with particles, but optical inspection by itself is not calibration.

Finally, data quality is the key for the benefit of the device manufacturer, the regulatory community and the end users of the drug devices—a win-win for all involved.

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