Quality requirements for cascade impactors assigned to batch release testing of a specific drug product; Part I: A grassroots look

The first of two articles describing a new approach to quality requirements for cascade impactors

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Caution: *This is the first of two articles in a series being published for purposes of education. Readers are advised that that the approach and methods for impactor quality testing described herein are not the current, established methods. Any change to established methods would require validation and adoption by the community at large, including the relevant regulatory agency or agencies, especially for use with registered drug products.*

There has been significant progress on the subject of impactor quality control in the past 20 years.

Examples include:

1. an impactor (the Next Generation Impactor, NGI™) designed according to known impactor principles, with quantitative nozzle dimensional specifications, calibrated with particles, and with stainless steel nozzle pieces;
2. more widespread use of stainless steel for Andersen impactors;
3. publication in the USP of quantitative nozzle dimensions for the Andersen impactor as well as the NGI;
4. publication of a sensible averaging method ("effective diameter") to assess impactor nozzle quality during periodic optical mensuration; and
5. micron- or sub-micron-precision optical measurements of nozzles.

All of these aspects are good and smart steps forward towards high-quality, in-use impactors. And everyone knows that impactor quality comes about by keeping the nozzles of each stage clean and unchanged over time during use. So, what is there to talk about? Plenty!

Impactor quality requirements today tell us that the nozzle diameters are in a certain range, but the batch release criteria relate to the mass of active pharmaceutical ingredient (API) on impactor stages or groups of stages. So, how can we know that the nozzle diameter ranges are not so large that the uncertainty in the impactor results exceeds the allowed range of API given in the batch release criteria? Or is it the other way around—that is, the allowed nozzle diameter range is so small that users are wasting effort keeping their impactors so perfect, because possibly a much wider range of nozzle diameters would still easily test the batch release criteria.

To begin to unravel these remarks, consider how we use an ultraviolet/visible spectrophotometer to measure the concentration of an active pharmaceutical ingredient (API) in a solution. We have calibrated and maintain this instrument. But more importantly, when testing for a "yes/no" decision about releasing a batch of drug product to the public, we have chosen the calibration conditions to show that the instrument is sufficiently accurate with small enough uncertainty that the measured value gives a confident assessment of whether a batch of the drug product is suitable for release. Indeed, usually measurement of more than one product attribute goes into such a decision, requiring confidence in each instrument that is involved.

The thesis presented here is that questions about accuracy and uncertainty of cascade impactor *results* have not been articulated by the inhaler testing community and that, consequently, producers today hold their cascade impactors to quality criteria that may be neither necessary nor sufficient for a confident batch release decision.

This first article in a two-part series takes a "fundamental" or "grassroots" look, therefore, at the question of how to create both necessary and sufficient quality requirements for cascade impactors that are used for batch release testing of a specific drug product. The thought process applies to devising meaningful impactor quality requirements when testing an existing drug product or when developing a new drug product, but focuses here on batch release testing of *existing* drug products.

Batch release testing with an impactor

There will be a number of analytical instruments from which the manufacturer obtains data to determine whether a batch of drug product is suitable for release to the public. In each case, the measurements that must be made for batch release and the instruments necessary for each measurement are spelled out in the agreed-upon approval package, or dossier, issued by regulatory authorities (e.g., United States Food and Drug Administration, European Medicines Evaluation Agency) to the applicant. Indeed, the alert applicant, early in the process, will have identified a Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQAs) aimed at achieving this profile, and at the time of approval, there should be no surprises in the CQAs that must be met in the batch release testing.[1]

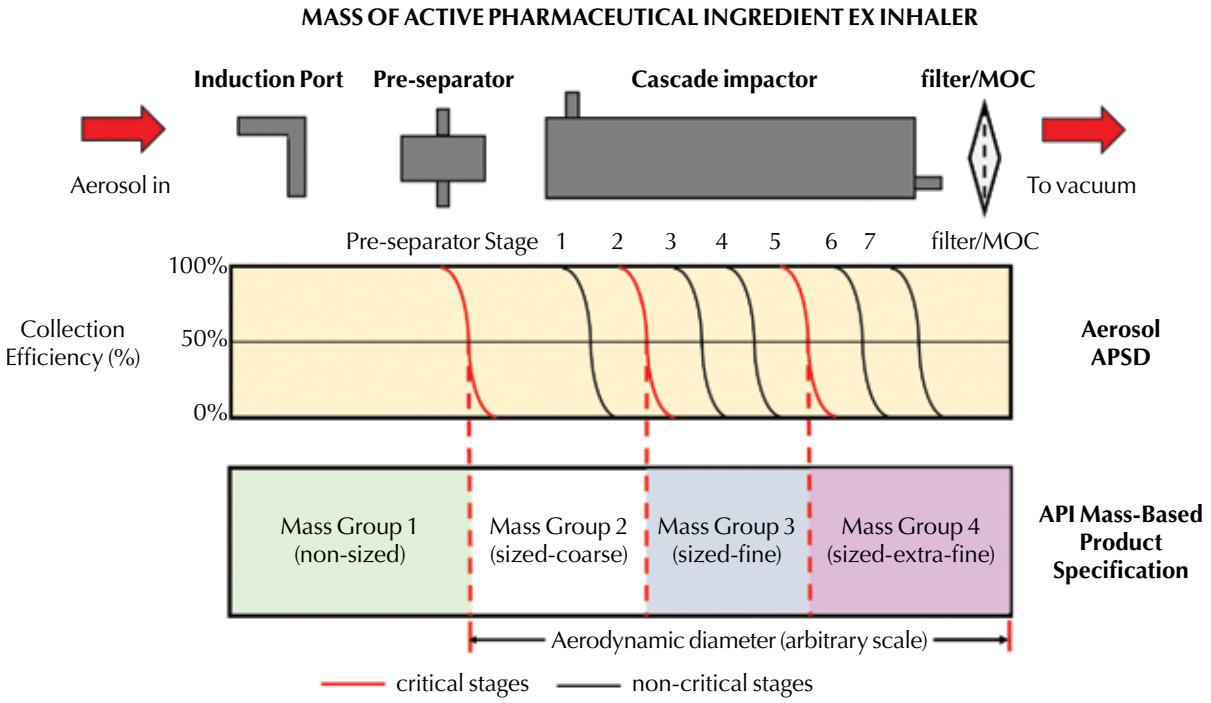
Each CQA has a pass/fail criteria associated with it and one or more instruments used to make the determination of whether the CQA is met. The accuracy and precision of the instruments must be sufficient to make a confident determination. Therefore, the instruments must be maintained sufficiently to be known to function to the required accuracy and precision. The necessary and sufficient quality specifications for each instrument are, then, designed and expressed to meet these accuracy and precision requirements, daily and reliably.

So, why has this mental and practical exercise *not happened* for cascade impactors? Or has it? After all, the USP guidelines for impactor quality control[2] indicate that periodic optical inspection of the nozzles is the proper approach. But upon closer scrutiny, the USP discussion of this subject appeals only to the intuition and says, essentially, that "periodic" optical inspection is surely *necessary*. So, periodic optical inspection of impactor nozzles is the common practice, measuring all nozzles on all stages of an impactor, usually annually, and to the micron-level precision now available in commercial vision systems. Impactors so maintained, to the original manufactured quality, are widely regarded to be the best instruments available for the purpose.

Let's assume, for the purpose of argument, that impactors so maintained are the best available technology, representing the state-of-the-art. We still have the responsibility to ask whether this best available technology is necessary or not, whether it is sufficient or not, or whether it is neither necessary nor sufficient for batch release testing of a registered drug product. It is a proper expectation that the specifications for any piece of analytical equipment are both necessary and sufficient specifications. For historical reasons, this proper expectation is yet to be applied to cascade impactors.

Figure 1

Typical stage groupings. An aerosol emitted by a dry powder inhaler into the NGI can be grouped logically into four segments (from Reference 3, used with permission).



It is best to start our examination of necessity and sufficiency by looking at the batch release specifications themselves because these specifications tell us what the instrument must do. Typically, the agreed-upon, impactor-based particle sizing requirements for a product undergoing batch release testing have to do with groups of stages; that is, the mass collected in several NGI cups or on several Andersen plates are added together and are expected to be in a given range. Figure 1 shows a typical stage-grouping exercise, based on testing a dry powder inhaler (DPI) with the NGI.[3] Testing with the NGI is especially helpful because its pre-separator has a known efficiency for particle capture.[4] Consequently, the impactor stages can be divided into three logical groups with known boundaries for the sizes of particles in those groups, along with one group that does not have known particle-size boundaries. (This group includes the induction port, which is a component with ill-defined particle capture characteristics.)

Table 1 displays the characteristics of the stage groupings and, to give firm values to the particle sizes in each group, the inlet flow rate to the NGI is considered to be 60 L/min. Immediately, we see that there are only three D50 values that matter to the masses captured in the individual groups, namely D50 for the pre-separator, Stage 2 and Stage 5. So we have to ask what that indicates about nozzle inspections. For one thing, the six nozzles on the inside of the pre-separator (each 12.8 mm ± 0.05 mm) and the six nozzles on Stage 2 (each 4.88 mm ± 0.04 mm) are easy to inspect with pins (e.g., class X go-no/go pins from Vermont Gage, Swanton, VT, US). Purists will say that inspecting with pins is not enough because an elliptical nozzle can pass a pin test and yet be unacceptable; however, in this context, we are speaking of used impactors; so we rely on the manufacturer to determine that the nozzles are sufficiently round when the impactor is new.[5] So, the reality is that in 10 minutes, a technician can determine if two of the three key nozzle sets are within specifications or not. *Therefore, annual optical inspection of two of the three key nozzle sets is seen to be unnecessary*—although evaluation of Stage 5 is still essential.

And what about Stage 5? There are 152 nozzles, each 0.608 mm ± 0.01 mm in diameter. It would be onerous to inspect these nozzles with pins on a regular basis, although technically, it can be done. Maybe annual optical inspection of these nozzles is still the best approach. Or, very possibly, regular measurement of pressure drop across Stage 5 would be sufficiently accurate to indicate whether the nozzles are "okay."[6]

First, let's ask what "okay" means. For this purpose, we look at the batch release specifications. For any given product, batch release specifications are agreed upon by the manufacturer and the regulatory agency and articulated as CQAs in the dossier that accompanies the permission to manufacture for sale to the public. But, for discussion purposes, we assume that the specified mass in each group is allowed a range of ± 10%. Further, to demonstrate a specific case, we assume that the incoming aerosol is log-normally distributed with a mass median aerodynamic diameter (MMAD) of 2.0 microns and a geometric standard deviation (GSD) of 2.0. This aerosol has 12.0% of its mass in Group 2, 73.8% in Group 3, and 13.8% in Group 4 when the impactor nozzles are their nominal dimensions (more complex details, such as impactor-sized mass described in reference,[7] will be included in the second article in this two-part series). And since the nozzles on Stage 5 are the only ones that we have to worry about (experience indicates that the nozzles on the pre-separator and on Stage 2 do not fail inspections), we are able to plot how the mass in each group changes with changes to the

Table 1

Four Groups of Impactor Components for Assessing DPI Performance

Group Number and Name	Components in Group	Particle Size Range # (60 L/min Inlet Flow)	Nominal Diameters of Nozzles (mm)
1—Non-Sized	Induction Port, NGI pre-separator	Not Defined*	12.8 (pre-separator)
2—Coarse	Stage 1 and 2	4.46 to 12.8	14.3, 4.88
3—Fine	Stage 3, 4 and 5	0.94 to 4.46	2.185, 1.207, 0.608
4—Extra Fine	Stage 6, 7 and micro-orifice collector (MOC)	Smaller than 0.94	0.323, 0.206, 0.070

#D50 values of stages on border of groups[3]
*Induction port collects mostly "large" particles, but because of turbulence is also able to collect small particles and with an ill-defined efficiency; the NGI pre-separator has a well-defined collection efficiency, capturing nearly all particles larger than 12.8 microns, when the flow rate is 60 L/min.

diameter of the Stage 5 nozzles. We note first that the mass in Group 2 does not change when the nozzles on Stage 5 change. That means that the mass on Groups 3 and 4, summed together, always equals 87.6% of the aerosol mass. So, when we let the nozzle diameters change on Stage 5, we immediately see the effect on the Group 3 and 4 mass (Figure 2; the math for this exercise is given in equations 1 and 6 of reference 8).[8]

If the Stage 5 nozzles change in size, the D50 value shifts slightly, and any mass no longer in found in the cups that define Group 4 must appear in Group 3 (and vice versa); but this mass change is a larger fraction of the Group 4 mass than it is of the Group 3 mass. Therefore, the batch release constraints on Group 4 (nominal ± 10%) provide the more rigorous constraints on the acceptable limits for the diameter of nozzles on Stage 5, thereby defining the acceptable limits for Stage 5 nozzles. Further, these *necessary* constraints on the Stage 5 nozzles depend on the aerosol itself, which is shown in Table 2. Moreover, Table 2 demonstrates that the smaller the aerosol, the larger the fraction in Group 4, so that a small shift in Stage 5 nozzles becomes less important. The opposite is also true, which is why an aerosol with an MMAD of 2.5 microns (and GSD of 2.0) puts tighter constraints on Stage 5 nozzles than the aerosol on which Figure 2 is based.

Now, we see that the nozzle specifications, when derived from the batch release specifications, depend on the aerosol that we are measuring—a very logical and satisfying outcome. Not only have we quantified the *necessary* limits of allowable nozzle diameters, but we have shown that, in practice, we must control essentially only Stage 5 because a) the pre-separator and Stage 2 are trivial to maintain and b) the stage groupings dictate that Stage 5 is the only stage that matters besides the pre-separator and Stage 2. We emphasize that the constraints shown in Table 2 are *necessary* constraints, and we postpone briefly the discussion of *sufficiency*.

The calculations behind Figure 2 and Table 2 are examples; and much remains to be laid out to implement this approach for inhalable aerosols in general. For example, there are simple constraints on all of the other stages in the impactor, too, but ones that are readily met and trivial to maintain.[1] (More complete examples of these principles will be provided in the second article.)

Pressure drop/Flow resistance

Question: What could be easier than reducing the impactor quality issues to a single stage, namely Stage 5? Answer: Measuring pressure drop of Stage 5, instead of using optical inspection of its 152 nozzles. This approach has been described by previous investigators and appears to have matured to a practical level.[6,9,10] The USP and manufacturer's constraints on Stage 5 nozzles are 0.608 mm ± 0.01 mm. The constraints given in Table 2 are less stringent. This means that the accuracy and precision required of the pressure drop measurements are relaxed compared to those necessary for maintaining nozzles to the USP/manufacturer standards.[4] Table 3 shows that the range of pressure drop across Stage 5 that will indicate whether Stage 5 meets the current USP requirements and the requirements derived from the batch release specifications (as given in Table 2). Here, we have used the principle that the pressure drop depends on the fourth power of the nozzle diameter.[10] Differential pressure transducers that measure this range to an accuracy of 1% are readily available (e.g., the TruStability™ HSC series by Honeywell, Golden Valley, MN, US; and the DLVR series by All-Sensors, Morgan Hill, CA, US).

Figure 2

Change in mass of Groups 3 and 4 when Stage 5 nozzles change. Batch release specifications for Group 4 control the limits of acceptable Stage 5 nozzle diameters. In this example, the aerosol has an MMAD of 2.0 microns and a GSD of 2.0.

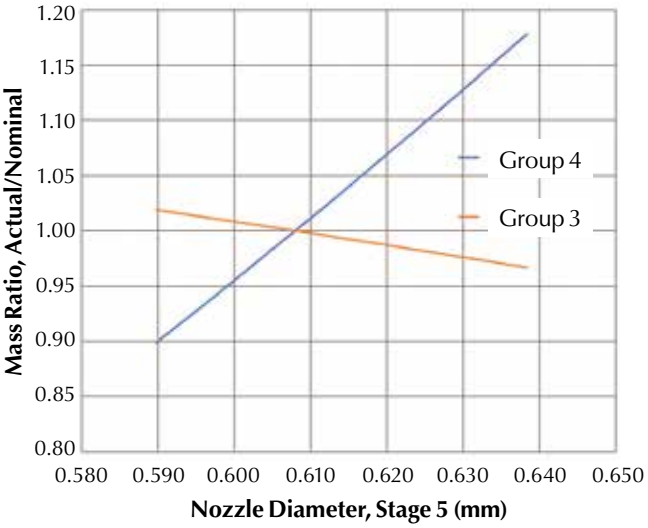


Table 2

Necessary Constraints on Stage 5 Nozzles for Example Aerosols

MMAD (micron)*	Maximum Acceptable Nozzle Size (mm)	Minimum Acceptable Nozzle Size (mm)
1.5	0.629	0.587
2.0	0.626	0.590
2.5	0.623	0.593

*GSD is 2.0 in all cases

Table 3

Range of Allowable Pressure Drop on Stage 5 for Given Nozzle Diameter Specifications

Aerosol MMAD (micron)	Maximum Acceptable Nozzle Diameter (mm)	Minimum Acceptable Nozzle Diameter (mm)	Minimum Acceptable Pressure Drop (Pa)	Nominal Pressure Drop (Pa)*	Maximum Acceptable Pressure Drop (Pa)
1.5	0.629	0.587	443	507	584
2.0	0.626	0.590	451	507	572
2.5	0.623	0.593	460	507	560
USP Specs	0.618	0.598	475	507	542

*from reference 6

So, when the batch release specifications are allowed to drive the impactor quality specifications, it is entirely possible that the user could periodically measure the pressure drop (delta P) of Stage 5, with readily available transducers, and never send his or her impactor out for optical inspection. Another advantage of frequent delta P measurements is that, in the event that a set of nozzles are found to be out of specifications, the potentially affected tested data since the previous in spec measurement would be rather limited, reducing the work of the impact analysis.

Measurement uncertainty, analytical power and sufficient nozzle diameter constraints

So far, we have described how batch release specifications lead to *necessary* constraints on the nozzle diameters. Now we tackle the more thorny question of *sufficient* constraints. Here, we must ask if the uncertainty in the measurement instrument is small enough to make a confident decision that a measured value satisfies or fails a specification. In the worst case, the instrument uncertainty is larger than the specification range that it is meant to test, a result that would mean that the instrument is not fit for the purpose of testing the batch release specification (i.e., the user needs a different instrument). This confidence or lack thereof can be captured in the concept of analytical power, which we define as the ratio of the specification span to the uncertainty in any individual measurement. The minimum acceptable value of the analytical power is 1.0; ideally, the analytical power is 10 or more, and a value smaller than 1.0 means the instrument is not fit for purpose. For a registered drug product, there are likely a variety of non-idealities, and it is difficult to revisit batch release specifications to make improvements. For a new drug product, the user should negotiate proper batch release specifications with specific instrumentation in mind so that the analytical power is clear and agreed upon with the relevant regulatory authorities.

The content presented so far discusses how wide a nozzle diameter range, starting from nominal, one can allow and not change the mass in Group 4 by more than ± 10%, thereby meeting the batch release specifications, but *under the assumption* that the aerosol itself has not shifted. (The more complex problem must consider that the nozzle diameters are not nominal at the outset, an analysis that will be discussed in a later article.) But we must ask "what happens if the aerosol has changed *and* the nozzles have changed?"

The simple fact, perhaps surprisingly, is that the answer to this question has not appeared in public literature, although this author wishes otherwise.

The root cause of the absence of this analysis is likely that the following question has not been clearly addressed: Do we want a well-controlled mass of "extra fine" particulate matter consisting of, *nay defined as*, particles smaller than the nominal D50 value of Stage 5? Such a requirement would logically be connected to the therapeutic value of the drug product and is very likely the intent of the inhaler manufacturer and the regulatory agency that approved the inhaler. Yet, very possibly, some disagreement on this point exists in the inhaler testing community.

Assuming, however, that controlling the extra fine mass *is indeed the objective*, we must recognize that false positives and false negatives are both possible with today's impactor quality specifications (and ultimately will be possible with any impactor quality specifications). A false positive (Type II error) would mean that the mass of "extra fine" particulate matter, as measured by summing the mass captured in Stages 6 and 7 and in the micro-orifice collector (MOC), remains within the expected ± 10%, even though the mass of aerosol smaller than the nominal D50 value of Stage 5 decreased or increased by more than 10%—a condition that would occur only if the nozzles on Stage 5 moved in the opposite direction. The false negative scenario (Type I error) would be the mass captured in Stages 6 and 7 and the MOC changing by more than the expected

10%, even though the mass of aerosol smaller than the nominal D50 value of Stage 5 decreased or increased by less than 10%—a condition that would occur only if the nozzles on Stage 5 moved in the same direction.

Fast forwarding the logic trail, it quickly becomes apparent that *sufficiency* in the setting of specifications for impactor nozzles must derive from an agreed-upon target for the probability of false negatives and the probability of false positives, as related to the mass of aerosol in given size ranges since no instrumentation or method has absolutely zero probability of Type I or Type II errors.

The current approach to impactor quality specifications makes no reference to Type I or Type II errors as related to mass of aerosol in given size ranges, only in reference to the impactor aerodynamics themselves.[11] *So, much work remains to establish impactor specifications suitable for batch release tests that are based on size-fractionated aerosol mass.*

Conclusions

Readers involved with testing according to Good Manufacturing Practices will recognize that it will be many years before the methods proposed here are in general practice. In that regard, each user who is testing an existing drug product should and must continue, day after day, with the established GMP procedures for that drug product. Inhaler manufacturers are free to experiment with the approach described here but not with batches to be released to the public. In doing this experimentation, it is likely that product-specific methods will be developed; once these methods are validated, they can become part of the routine of quality control for impactors used in that product's batch release testing.

So, let us be optimistic—by taking a grassroots look at the batch release specifications and the philosophy that we want necessary and sufficient impactor specifications for making a yes/no decision about specific batch release requirements, it may be possible to reduce the work of impactor quality control substantially. That is, only some nozzles are important to most batch release testing. And in many cases, some key nozzles are trivial to maintain in their original state and to measure readily with high-accuracy pins. And there will be, in many cases, only one impactor stage that needs regular optical inspection. Finally, with the maturity of the pressure drop method, frequent checks of the suitability of the nozzles of this one key impactor stage are now practical, facilitating a high degree of confidence in the quality of these nozzles on a continual basis.

Further, we have noted that the *necessary* nozzle specifications for this one key stage are likely to be broader than those of the current USP specifications. This result can benefit a producer who may seek to expand the acceptable nozzle diameters. But maintaining the USP specifications reduces the probability of Type I and Type II errors; so it may be that the most benefit to some producers will be to maintain or even tighten the USP specifications, reduce the probability of Type I and Type II errors, and measure with pressure drop on a regular basis to assure the attainment of these probability goals (an assurance not possible with annual optical inspection).

Quantitatively sufficient impactor nozzle diameter specifications currently elude the community of inhaler testers but must be based properly on quantifying the acceptable rate of Type I and Type II errors when testing for batch release. This analysis awaits a future publication.

Finally, the article has emphasized testing of existing drug products where the batch release specifications are already established. Ideally, all of these questions would have been asked during new product development so that the answers would enable batch release specifications that are both meaningful and measureable and properly agreed upon by the regulatory authorities, thereby enabling confident batch release testing to take place throughout the life of the drug product. Hopefully, when we look back 20 years from now, we will see some new drug products that have followed this logical path.

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