Quality requirements for cascade impactors assigned to batch release testing of a specific drug product; Part II: The concept of "sufficient" as applied to impactor quality specifications

The second article in a series describing a new approach to quality requirements for cascade impactors

Daryl L. Roberts, PhD[a] and Jolyon P. Mitchell, PhD[b]
[a]Applied Particle Principles, LLC
[b]Jolyon Mitchell Inhaler Consulting Services, Inc.

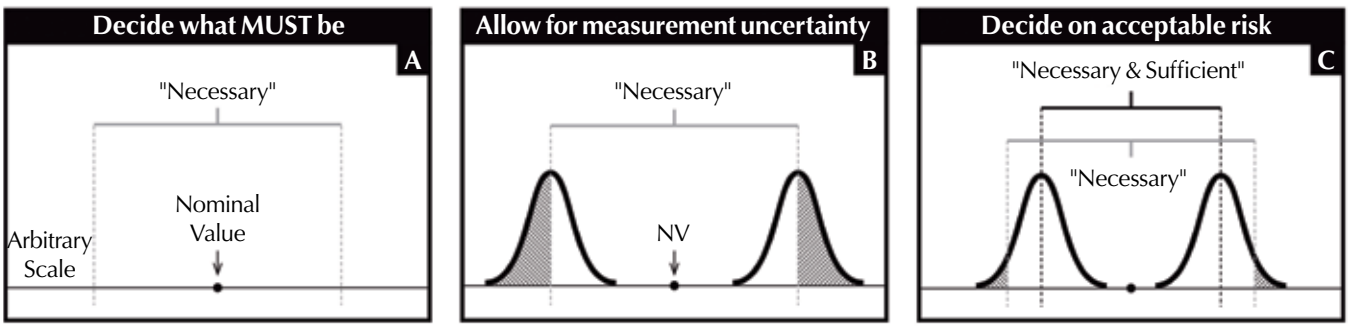
Caution: *This article is the second in a series being published for purposes of education. Readers are advised that the approach and methods for impactor quality testing described herein are not the current, established methods. Any change to established methods would require validation and adoption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

The multi-stage cascade impactor remains the primary measurement apparatus for the assessment of aerosol aerodynamic particle size distribution (APSD) of orally inhaled products (OIPs) because the mass of active pharmaceutical ingredient(s) is directly determined in relation to the clinically important measure of particle size, which is aerodynamic diameter. In the first article of this series, we examined how the batch release criteria for an OIP provide a means of determining the most broad quality specifications (based on stage nozzle effective diameter) that these impactors can have; i.e., the necessary specifications (Figure 1A). Since we based these specifications on the batch release criteria which themselves are aimed at ensuring product safety and efficacy, when impactors are on the edge of these specifications, the human health risk attributable to the aerosol particle size distribution is at its maximum.

Now, we ask: Is that situation acceptable? Put another way: are these *necessary* specifications *sufficient* to achieve an acceptably low risk (Figure 1B)? If so, we observe that the situation is fully in control, because the *necessary* conditions are also *sufficient*! Alternatively, we ask: Do the specifications need to be tighter to

Figure 1

Necessary and Sufficient Specifications
Necessary specifications give way to necessary and sufficient specifications as one assesses and manages risk.



achieve an acceptably low risk (Figure 1C)? If so, then we contend that these *sufficient* conditions will also satisfy the *necessary* conditions, again achieving the goal of both necessary *and* sufficient conditions. We intuitively seek this situation, where the impactor specifications are both *necessary* and *sufficient* (Figure 1C). That goal is ideal—and worth paying for; cost negotiation itself helps define the level of acceptable risk (which would be a separate and lengthy discussion).

In this article, we extend the thinking about defining the path to necessary and sufficient impactor quality specifications. We introduce the need for a careful definition of sufficiency. This definition, in turn, necessarily introduces the concept of acceptable risk. We have therefore set out the philosophy of establishing impactor quality specifications that are *sufficient* for meeting the batch release criteria for an OIP, although, in general terms, this same philosophy could potentially apply to the development of a control strategy for all new drug products based on measures of their critical quality attributes (CQAs). Ideally, the methodology will guide the developers of new OIPs so they can make sound proposals regarding impactor quality specifications to the appropriate regulators. In turn, regulators need to assure that the specifications for many instruments, of which cascade impactors are only one, are both necessary and sufficient for batch release testing in quality control.

Stage grouping as a batch release test

A practical example based on testing an OIP with the Next Generation Impactor (NGI™) will serve to illustrate the principles involved. As discussed in the first article,[1] a typical batch release test is one that determines whether the sum of the mass of the active pharmaceutical ingredient (API) recovered from the collection cups of several neighboring stages of the cascade impactor, as part of the stage grouping data reduction process currently favored by US and European regulatory agencies,[2,3] is in a specified range. For example, as illustrated in Figure 2, the following four logical groups can be identified:

1. the non-sized fraction
2. the coarse fraction
3. the fine fraction
4. the extra-fine fraction

Table 1 indicates the size of particles in each of these fractions when the test is performed at a flow rate of 60 L/min and when the impactor nozzle diameters are at their nominal values, as defined in Chapter <601> of the United States Pharmacopeia.[6] The quality specifications for the pre-separator, Stage 2 and Stage 5 are the most important to consider further because each is located at a boundary between neighboring groups.

Following the approach described in the first article, we say that the batch release specifications should drive

Figure 2

Typical Stage Groupings

An aerosol emitted by a dry powder inhaler into the NGI can be grouped logically into four segments. (From Roberts and Mitchell,[4] used with permission.)

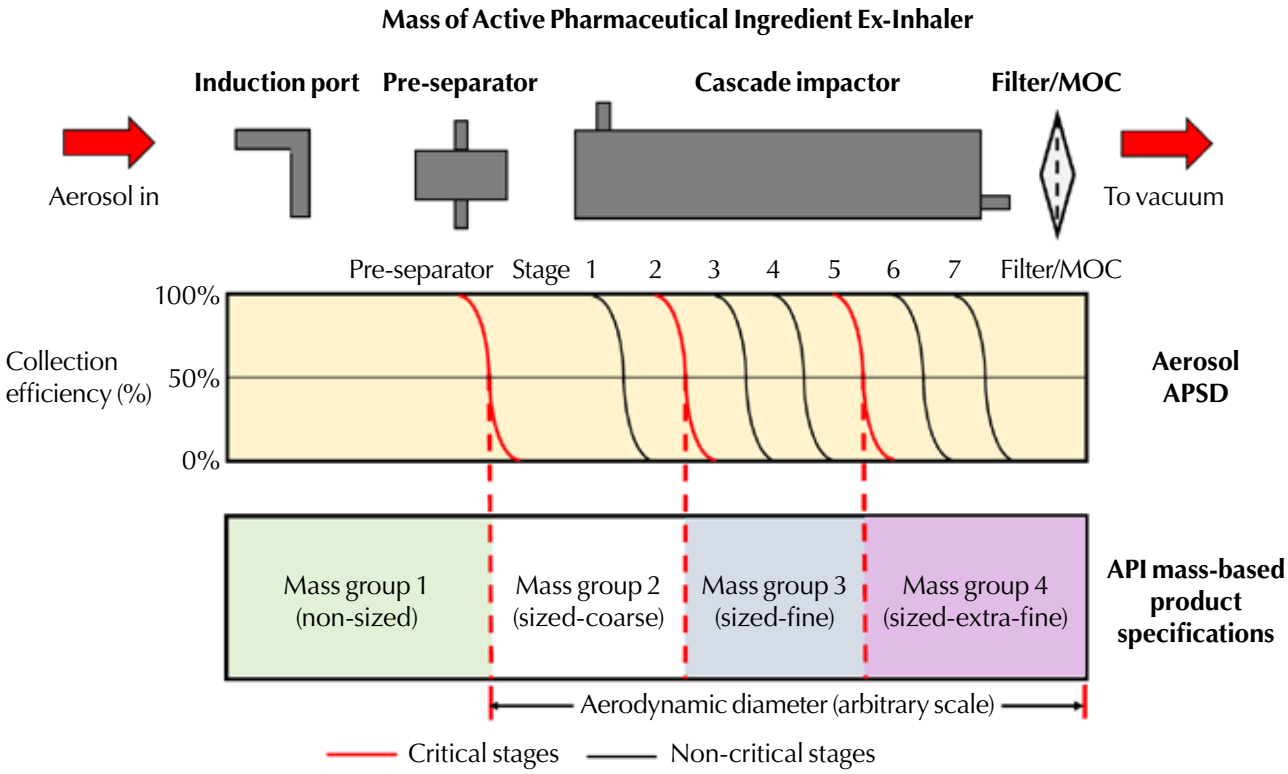


Table 1

Four Groups of Impactor Components for Assessing DPI Performance

Group Number and Identity	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	Stages 1 and 2	4.46 to 12.8	14.3, 4.88
3—Fine	Stages 3, 4 and 5	0.94 to 4.46	2.185, 1.207, 0.608
4—Extra-Fine	Stages 6, 7 and MOC	Smaller than 0.94	0.323, 0.206, 0.070

Stage cut-point sizes (D_{50}) are located at the border between neighboring groups.

*The induction port collects mostly "large" particles, as well as the ballistic fraction having high velocity (inertia) emitted from pressurized metered dose inhalers, but because of the presence of turbulence, is also able to collect small particles with an ill-defined efficiency.[5]

**The NGI pre-separator has a well-defined collection efficiency, capturing nearly all particles > 12.8 µm aerodynamic diameter, when the flow rate is 60 L/min.

the impactor quality specifications. These specifications for any given OIP 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. For discussion purposes, we assume that the specified mass in each group is allowed a range of ± 10% of the nominal value, but our approach would apply equally if a different range were allowed. Further, to demonstrate a specific case, we assume that the incoming aerosol is uni-modal and log-normally distributed, with a mass median aerodynamic diameter (MMAD) of 2.0 µm and a geometric standard deviation (GSD) of 2.0 (although a similar analysis would apply to OIP-emitted aerosols having other values of MMAD and GSD). When the impactor nozzles are their nominal dimensions and the flow rate is 60 L/min, this aerosol will deposit 12.0% of its API mass in Group 2, 73.8% in Group 3 and 13.8% in Group 4. The acceptable results for passing the batch release testing are given in Table 2, based on these values of nominal mass deposition with the associated tolerance of ± 10%.

At this point, we depart from the logic trail that we followed in the first article, wherein we looked at only the necessary impactor specifications. Now we ask: Are these necessary specifications also sufficient? The thought process for answering this question reveals one positive outcome as well as the key difference between the question of what constitutes "necessary" and what establishes "sufficient" specifications.

The positive outcome derives from the fact that the manufacturer specifications for new pre-separator nozzles and new Stage 2 nozzles are, by virtue of their relatively large effective diameters,[7] trivial to measure and maintain, ***and*** *are sufficient* to reveal whether a given aerosol satisfies the batch release critieria. The test of sufficiency comes from looking at the extremes of the cut-off diameter (D_{50}) values implied by the manufacturer specifications. Table 3 lists the nozzle diameter specifications and shows how the extremes of these specifications affect the size of particles retained at that point in the impactor.

The greatest shift in the measured mass of API contained in Groups 2, 3 and 4, caused by a movement

Table 2

Upper and Lower Limits for Passing Batch Release Testing for Example Case*

Group Number and Name	Mass of API in Given Group (%)
1—Non-Sized	—
2—Coarse	10.8 to 13.2
3—Fine	66.4 to 81.2
4—Extra-Fine	12.4 to 15.2

*Log-normal incoming aerosol with MMAD of 2.0 µm and GSD of 2.0; impactor inlet flow rate of 60 L/min

Table 3

Necessary Specifications for Nozzle Sizes for Example Case*

Component or Stage	Nozzle Diameter Specification# (mm)	Range of D_{50} Value (µm)
Pre-Separator	12.8 ± 0.05	12.73 to 12.88
2	4.88 ± 0.04	4.41 to 4.51
5	0.608 ± 0.018	0.899 to 0.982

*Log-normal incoming aerosol with MMAD of 2.0 µm and GSD of 2.0; impactor inlet flow rate of 60 L/min

#Manufacturer specifications for new pre-separator nozzles and new Stage 2 nozzles; necessary effective diameter range for Stage 5 as calculated by Roberts.[1]

in the underlying APSD, will occur at the extremes of these ranges of D_{50} values. If we calculate the change in the mass of API in each group, we find that the batch release specifications are met, as shown in Table 4 for the product MMAD and GSD parameters previously specified. (This underlying theory is summarized by equation 3 of Roberts and Mitchell.[4]) So, we can confirm that the manufacturer specifications for the pre-separator and Stage 2 are sufficient for the batch release test. Recall that manufacturer specifications essentially represent a "state-of-the-art" limit. If such technology were to fail the sufficiency test, the instrument would be deemed "unfit for purpose." Very likely, the NGI manufacturer specifications for the pre-separator and Stage 2 would pass this sufficiency test for a wide range of OIPs, simply because these specifications call for an uncertainty in the nozzle diameters that is less than 1% of nominal. Nevertheless, we observe that the inhaler testing community frequently errs by assuming this certitude exists without doing the calculations to confirm whether sufficiency has been met.

Two scenarios (Table 4) must be considered because it is not possible for all stage groups to meet their maximum ranges simultaneously nor their minimum ranges simultaneously. This result stems from the fact that each D_{50} value influences two stage groupings. Even though there are three stage groupings, there are only two, not three, independent variables. Therefore, to test the limits, neighboring groups must be in opposite extremes (max/min/max and min/max/min).

Table 4 reveals another important consideration: the necessary specifications for Group 4 are barely sufficient. Closer examination reveals that the calculation method for the necessary nozzle diameter (as discussed in the first article) is identical to the calculation method for the test of sufficiency performed to derive the values for Group 4 in Table 4. The reader may question if this approach is circular reasoning? The answer is "No," because we have ***not*** *taken into account any* ***uncertainty*** in the nozzle diameter measurements. It follows that, to answer the sufficiency question, we must assess the uncertainty in the measurements to which we attached the label "necessary." When we ask the question of necessity, we seek to find the limit of what the actual value must be. Of course, no real instrument perfectly reports the actual value of the item it measures. *With the question of sufficiency, we must therefore ask whether the uncertainty in the instrument performance (quantified in this case by the impactor nozzle diameters) creates an acceptable or unacceptable uncertainty in the CQA the impactor is intended to measure.*

Uncertainty, probability and type 1/type 2 errors

We must tackle the subject of measurement uncertainty in order to answer the question of sufficiency. This consideration dictates a quick detour into the world of error probability. The always-present finite measurement uncertainty reflects the fact that the instrument has a probability, rather than a certainty, of reporting the actual value. Truly random sources of uncertainty create a Gaussian shape to this probability profile. In such a profile, the peak in the distribution is the actual value, and the shape reflects the probability of the instrument reporting something other than this true result. Figure 3 displays a situation where the "in

Table 4

Change in Mass of API of Incoming Aerosol Having MMAD and GSD of 2.0 µm and 2.0, Respectively, in Each Group at Extremes of Necessary Nozzle Diameters

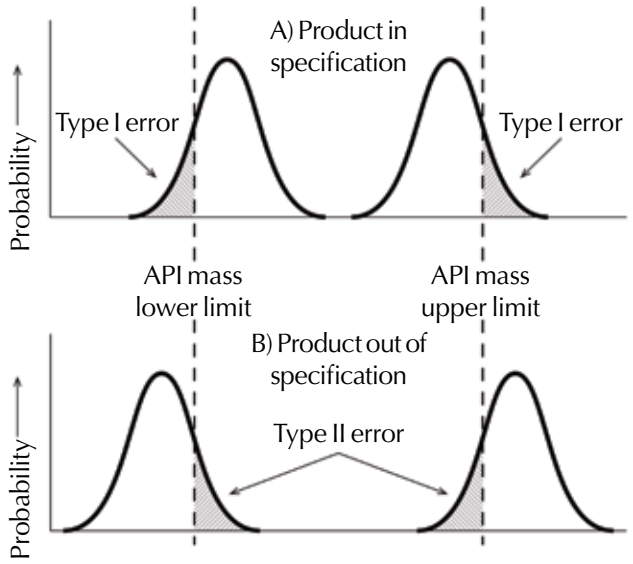
Scenario 1 Max, Min, Max			
Stage Grouping	**Range of D_{50} (µm)**	**Mass of API in Given Group (%)**	**Batch Release Specification (%)**
2	4.41 to 12.88	12.34	10.8 to 13.2
3	0.982 to 4.41	72.06	66.4 to 81.2
4	< 0.982	15.24	12.4 to 15.2

Scenario 2 Min, Max, Min			
Stage Grouping	**Range of D_{50} (µm)**	**Mass of API in Given Group (%)**	**Batch Release Specification (%)**
2	4.51 to 12.73	11.66	10.8 to 13.2
3	0.899 to 4.51	75.53	66.4 to 81.2
4	< 0.899	12.43	12.4 to 15.2

Figure 3

Type I and Type II Errors

The influence of instrument uncertainty on the uncertainty of mass of active pharmaceutical ingredient (API) in a group of stages.



specification" result lies between a lower limit and an upper limit of the mass of API in a given group of stages (such as Group 4 in the example shown in Figure 1 and Table 2). It is possible for an actual value to be inside the specification range, but because of random error, the instrument reports a value that is outside the specification range (top half of Figure 3).

This instance, called a Type I error, would cause an in-specification product to be considered unacceptable. The bottom half of Figure 3 displays the opposite situation where the actual value is outside the specification range, but because of random error, the instrument reports a value that is inside the specification range. This instance, called a Type II error, would cause an unacceptable product to be considered acceptable.

We now consider how the uncertainty in the nozzle diameters of Stage 5, in our example problem, contributes uncertainty to the mass of API in Group 4. (A completely general, comprehensive mathematical treatment for all circumstances is something we plan to describe in a future publication.) For this example problem, we have shown previously (in equation 12 of Roberts and Mitchell[4]) that propagation of error principles leads to a relatively simple expression for the relationship between the uncertainty in the D_{50} value of Stage 5 and the mass fraction of API in Group 4:

$$\sigma_{f_4}^2 = \left(\frac{\partial f_4}{\partial D_{50,5}}\right)^2 \sigma_{D_{50,5}}^2 = \left(R(D_{50,5})\right)^2 \sigma_{D_{50,5}}^2 \qquad [1]$$

Here, σ_{f4} is the uncertainty in the mass fraction of API in Group 4, $\sigma_{D_{50,5}}$ is the uncertainty in the D_{50} value of Stage 5 and $R(D_{50,5})$ is the slope of the cumulative size distribution evaluated at the particle size equal to the D_{50} value of Stage 5. For the purpose of communicating the method of answering the sufficiency question, the value of the coefficient, R, is not important because it can be divided by any scale chosen for the vertical axis; the qualitative features of any outcome are thereby preserved.

The important issue is recognizing how the uncertainty in $D_{50,5}$ relates to the measurement uncertainty of the nozzle diameters on Stage 5. This matter has been articulated in equation 39 of Roberts[7]:

$$\left(\frac{\sigma_{D_{50}}}{D_{50}}\right)^2 = \frac{1}{4}\left[\left(\frac{\sigma_Q}{Q}\right)^2 + \left(\frac{\sigma_W}{W^*}\right)^2\right] \qquad [2]$$

Here, σ_Q is the uncertainty in the volumetric flow rate of air, Q, coming into the impactor, σ_W is the uncertainty in the measurement of an individual nozzle diameter and W^* is the area-mean diameter. *Equation 2 conveys that uncertainty in D_{50} for any stage results from **both** flow rate uncertainty and nozzle diameter uncertainty.* As a consequence, impactor nozzle specifications are inherently entwined with flow meter specifications.

So, whereas we have been talking only about impactor quality specifications, it is evident that "sufficient" impactor nozzle diameter specifications will also be influenced by the quality of the flow rate measurement.

Combining equations 1 and 2 allows a simple expression for σ_{f4}:

$$\sigma_{f_4} = \left(\frac{\partial f_4}{\partial D_{50,5}}\right)\sigma_{D_{50,5}} = \frac{1}{2}\left(D_{50,5} * R(D_{50,5})\right)\left[\left(\frac{\sigma_Q}{Q}\right)^2 + \left(\frac{\sigma_W}{W^*}\right)^2\right]^{1/2} \qquad [3]$$

To appreciate the trade-off between nozzle diameter quality and flow rate measurement quality and the way measurement uncertainty will play a role in defining sufficient nozzle quality specifications, we show two curves in each half of Figure 4. In curve 1 (the dashed line in Figure 4A), we assume that the only random error is in the measurement of nozzle diameters and that the uncertainty reflects the range allowed for necessary nozzle specifications. The actual value of the mass fraction of API in Group 4 is at the peak of this curve and (for the sake of illustration) the value of σ_{f4} is large enough to produce a 2.5% probability of a Type I error (the shaded region). In curve 2 (the solid line in Figure 4A), we add a reasonable uncertainty in the flow rate measurement. The peak of the curve does not change but the size of the Type I error increases substantially. (We will soon see why the Type I error is substantially increased by a modest increase in the standard deviation of the curve). In summary, although consideration of the *necessary* nozzle diameters alone may introduce only a minor error probability (curve 1), inclusion of the flow rate uncertainty, which we contend to be the proper way to assess the situation, makes these necessary nozzle diameters *insufficient* (curve 2).

In curve 3 (the dashed line in Figure 4B), we have reduced the acceptable uncertainty in the nozzle

diameters, reflecting a tightening of the nozzle diameter specifications, compared with curve 1 (the dashed line in Figure 4A). These more stringent specifications reduce the standard deviation of the curve to the point at which there is a negligible probability of a Type I error. However, when properly combined with the flow rate measurement uncertainty (curve 4, the solid line in Figure 4B), the probability of a Type I error increases but to an amount that is acceptable (the shaded region). For the sake of illustration, we have shown curve 4 to be identical to curve 1 although this situation is not a requirement. *The take-away message from this example is that flow rate uncertainty reduces the acceptable uncertainty in nozzle diameters*. When these tighter specifications achieve a risk level that is deemed acceptable, they thereby establish both necessary and sufficient nozzle diameter specifications. In addition, we have demonstrated that there can be no "single answer" for defining necessary and sufficient nozzle diameter specifications because of the important influence of flow rate uncertainty.

Now the question becomes whether such shifts in the probability distribution of the mass of API on Stage 4 can reasonably take place with practical values of the flow rate uncertainty and the nozzle diameter uncertainty. To answer this question, we evaluate equation 3 for a practical range of the relative standard deviation of nozzle diameter and flow rate (and with the assumption that the quantity $\frac{1}{2} D_{50} R(D_{50})$ equals 1.0, for illustration purposes; note that the magnitude of this quantity is specific to a given aerosol APSD). We have chosen baseline conditions for the nozzle diameter uncertainty to have an RSD, expressed as a fraction, of 0.03 and the flow rate uncertainty to have an RSD of 0.02. We have also assigned a Type I error of 2.5% to this condition; that means that the lower limit of the API mass is two standard deviations away from the peak in the distribution. The rationale for selecting these baseline values of RSD is:

a) The necessary nozzle diameter range for Stage 5 is 3% of nominal (Table 3);

b) An accuracy for flow rate measurement within 2% of nominal is readily available in reasonably priced flow meters.

Two scenarios are illustrated in Table 5. In the first, the nozzle diameter uncertainty is taken as that of the necessary nozzle specifications from Table 3 (namely 3%). Here flow rate uncertainty does not much affect the probability of a Type I error until the flow rate uncertainty approaches equality with the nozzle diameter uncertainty; then the error probability increases further by a factor of almost five as the flow rate uncertainty enlarges from 2% to 5%.

The other scenario in Table 5 takes the nozzle diameter uncertainty to be that of the manufacturer specification for new Stage 5 nozzles (from Table 5 of Roberts and Romay[8]). Now the Type I error probability is neg-

Figure 4

How Measurement Uncertainty Tightens Impactor Quality Specifications

The nozzle specifications must be tighter (compare curve 3 to curve 1) so that the combined uncertainty resulting from nozzle measurement uncertainty *and* flow rate uncertainty (curve 4) controls the probability of failure to an acceptably small value.

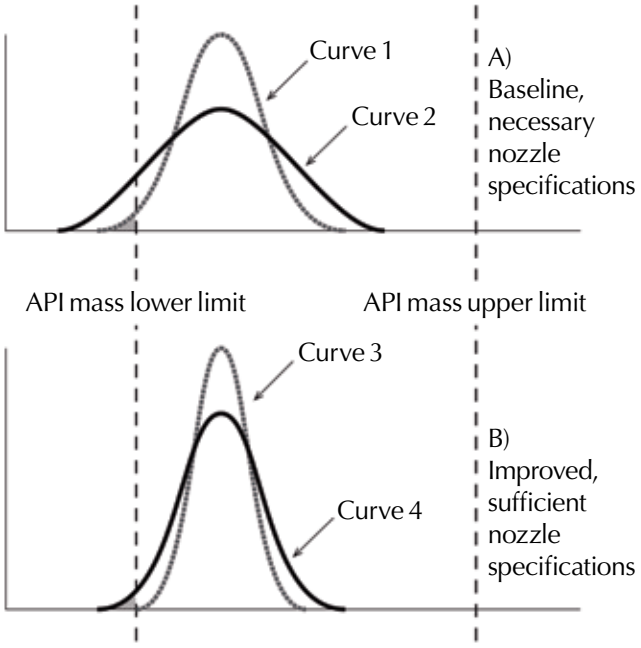


Table 5

Influence of Nozzle Diameter and Flow Rate Uncertainty on Type I Error Probability

Nozzle Diameter Uncertainty $\left(\frac{\sigma_W}{W^*}\right)$	Flow Rate Uncertainty $\left(\frac{\sigma_Q}{Q}\right)$	Type I Error Probability (%)
"Necessary"		
0.03	0.00	0.81
0.03	0.01	1.13
0.03	**0.02**	**2.28**
0.03	0.03	4.46
0.03	0.04	7.46
0.03	0.05	10.8
"Manufacturer Specification"		
0.016	0.00	3×10^{-4}
0.016	0.01	7×10^{-3}
0.016	0.02	0.24
0.016	0.03	1.70
0.016	0.04	4.71
0.016	**0.05**	**8.48**

ligible until the flow rate uncertainty exceeds about 3%, increasing to 8.5% when the flow rate uncertainty reaches 5%.

Today's compendial methods reflect manufacturer specifications for nozzles and allow as much as 5% uncertainty in the flow rate measurement.[6] The bold rows in Table 5 show that this condition is ill-advised because the probability of a Type I error under these conditions is about 4 times greater than that when the nozzle diameter specifications are relaxed to the "necessary" level and the flow rate is held to 2% uncertainty. Given the outcome from this analysis, it would be appropriate for stakeholders to adopt this easily achievable tighter control of flow rate.

Conclusions

We contend that measurement instrument quality specifications should be both necessary and sufficient and based on the batch release criteria themselves. The question of sufficiency introduces the concept of risk. In this article, focusing on the multi-stage cascade impactor used in assessment of emitted aerosol APSD in the context of OIP quality control, we have shown the path for quantifying the risk in terms of the instrument uncertainty, thereby defining the test for assessing sufficiency by relating this criterion to instrument measurement uncertainty. We have further shown that when the batch release criteria are based on the mass of API recovered from an impactor stage or group of stages, the measurement uncertainty associated with volumetric flow rate control must also be considered along with nozzle diameter uncertainty. We have further argued that users should be allowed to control *both* uncertainties in their most cost effective manner, so long as the specifications remain both necessary and sufficient. We conclude that the current measurement precision defined in the pharmacopeial compendia for flow rate control should be reexamined in this light.

The above analysis has concentrated on Type I errors, but a very similar story can be explained for Type II errors. We plan to include the assessment of Type II errors in a future publication along with a comprehensive mathematical approach.

We are hopeful that resourceful users will embrace this approach and make the case with regulatory agencies that the user should be allowed to propose impactor nozzle specifications and flow rate measurement specifications to achieve agreed-upon Type I and Type II error probabilities in each batch release test of aerosol particle size of an inhalable drug product.

Finally, we have emphasized testing of existing drug products, here, 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 shape 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 pathway in the course of their development.

References

1. Roberts, D. L., Quality Requirements for Cascade Impactors Assigned to Batch Release Testing of a Specific Drug Product; Part I: A Grassroots Look. Inhalation, 13(4), 10-16 (2019).

2. European Medicines Agency: Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products. EMEA/CHMP/QWP/49313/2005 Corr. 2006. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003568.pdf. Accessed August 20, 2019.

3. United States Food and Drug Administration. Draft Guidance for Industry: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products—Quality Considerations. Silver Spring, MD, US. 2018. https://www.fda.gov/downloads/drugs/guidances/ucm070573.pdf. Accessed August 20, 2019.

4. Roberts, D. L., J. P. Mitchell., Measurement of Aerodynamic Particle Size Distribution of Orally Inhaled Products by Cascade Impactor: How to Let the Product Specification Drive the Quality Requirements of the Cascade Impactor. AAPS Pharm. Sci. Tech., 20:57 (2019), https://doi.org/10.1208/s12249-018-1276-9.

5. Zhou, Y., J. Sun, Cheng Y-S., Comparison of Deposition in the USP and Physical Mouth-Throat Models with Solid and Liquid Particles. J. Aerosol Med. Pulmon. Drug Deliv., 24(6), 277-284 (2011).

6. United States Pharmacopeial Convention (USP). United States Pharmacopeia 41/National Formulary 36. Chapter <601>, Aerosols, Nasal Sprays, Metered-Dose Inhalers and Dry Powder Inhalers, 2018. USP, Rockville, MD, US.

7. Roberts, D. L., Theory of Multi-Nozzle Impactor Stages and the Interpretation of Stage Mensuration Data. Aerosol Sci. Tech., 43, 1119-1129 (2009).

8. Roberts, D. L., F. J. Romay., Relationship of Stage Mensuration Data to the Performance of New and Used Cascade Impactors. J. Aerosol Med., 18 (4), 396-413 (2005).

Daryl L. Roberts, PhD, is President of Applied Particle Principles, LLC, 17347 Westham Estates Court, Hamilton, VA, 20158, US, Tel.: +1 612 845-3293, droberts@particleprinciples.com, www.particleprinciples.com. Jolyon P. Mitchell, PhD, is President of Jolyon Mitchell Inhaler Consulting Services, Inc., 1154 Saint Anthony Road, London, Ontario, Canada, N6H 2R1, +1 519 472-5364, mitchelljolyon@gmail.com.

To read the first article in this series, "Quality requirements for cascade impactors assigned to batch release testing of a specific drug product; Part I: A grassroots look," please click here, visit the *Inhalation* home page or use the free article archive.