

Quality requirements for cascade impactors assigned to batch release testing of a specific drug product; Part III: Implications of Type II error probability

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

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Caution: This article is the third 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.

Unique attributes of cascade impactors, in particular their ability to collect size-fractionated samples of aerosolized active pharmaceutical ingredients (APIs), enabling direct determination of particle aerodynamic diameter, make them an essential tool for characterizing orally inhalable drug products (OIPs). Direct traceability to mass [1, 2] enables a measure of the aerodynamic particle size distribution (APSD), a characteristic that directly influences the safety and efficacy of any API [3]. Consequently, both manufacturers and regulators seek to ensure that commercially released inhalers generate aerosolized API mass in the same particle size range as that of the batches made for the clinical trials, enabling assurance of a safe and efficacious dose. Multi-stage cascade impactors uniquely enable this important measurement of the size-dependent, aerosolized API mass, both for clinical trials and for commercial release of product batches to the public [3, 4].

In Parts I and II of this series, we introduced the concept that the batch release criteria for OIPs can and should dictate the quality constraints on all cascade impactors (CIs) used for batch release testing [5, 6]. This logical proposition applies to the entire set of analytical equipment involved in the making and testing of a commercial drug product. However, the current approach to CI quality specifications requires only a verification of the diameter of nozzles of each stage along with a requirement that the flow rate during testing be known within ± 5% of a target value [7-9].

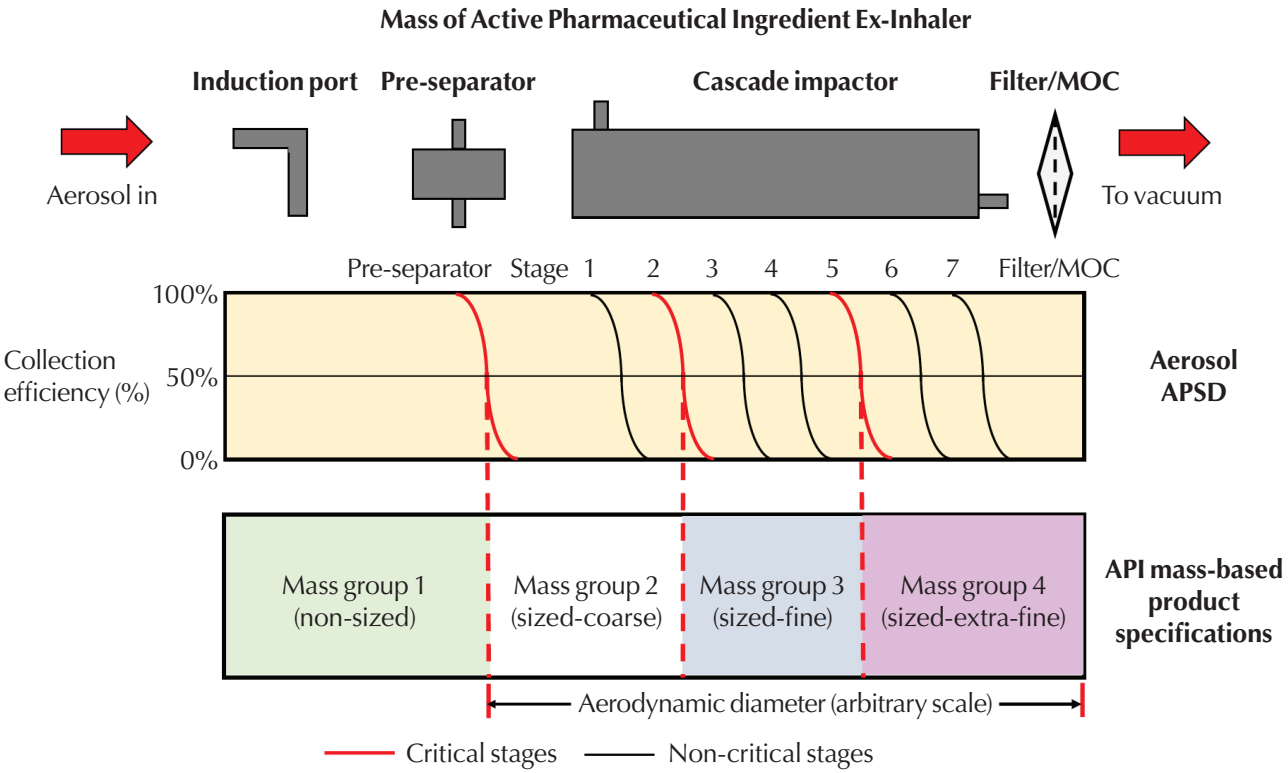
Here, we ask two questions: Are these requirements necessary? And are these requirements sufficient?

Our thesis is that the inhaler testing community, both from the manufacturer and regulator perspectives, should insist that the CI quality specifications be both *necessary* and *sufficient* for the testing of batches of drug product for release of that product to the public.

All necessary and sufficient specifications for CIs derive from the accuracy and precision of actual stage "cut-point" sizes (D_{50} values) during testing [10; see particularly equations 9, 10, and 11 of the article]. In Parts I and II, we explained the implications of *necessary* [5] and then of *sufficiency* in the context of managing Type I risk, that is, a probability of a batch of OIPs being rejected in quality control when in fact the batch is within the batch release specifications (BRS) [6]. In the current article we extend and complete the picture of setting necessary and sufficient impactor specifications by showing how the probability of making a Type II error is also related to cascade impactor specifications, "Type II" meaning a probability of a batch of OIPs being accepted when in fact the batch is outside the BRS.

Figure 1

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 [10], used with permission.)



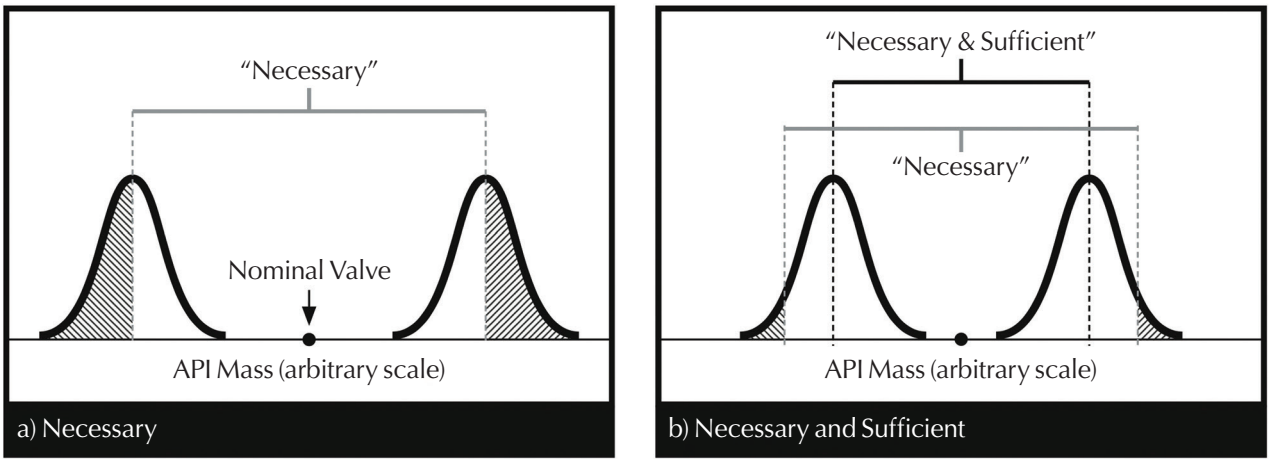
Review of Type I errors

It is quite helpful to review Type I errors and to keep a practical example in mind, so that the thought processes that follow will be realistic, as opposed to remaining theoretical constructs. As previously, we take as our example the measurement of the output of dry powder inhalers with a Next Generation Impactor (NGI), including its pre-separator, a common method following the methods for OIP APSD determination given in the pharmacopeial compendia [8, 9]. In this example, the batch release criteria are expressed as the mass of API inside each of four groups shown in Figure 1, [10] in accord with recommended practice of the United States Food and Drug Administration (FDA) [11].

Typical batch release requirements are based on the mass of API measured in each of these four groups within prescribed limits under test conditions that allow a quantitative knowledge of the aerodynamic size of particles collected within the individual stages.

Figure 2

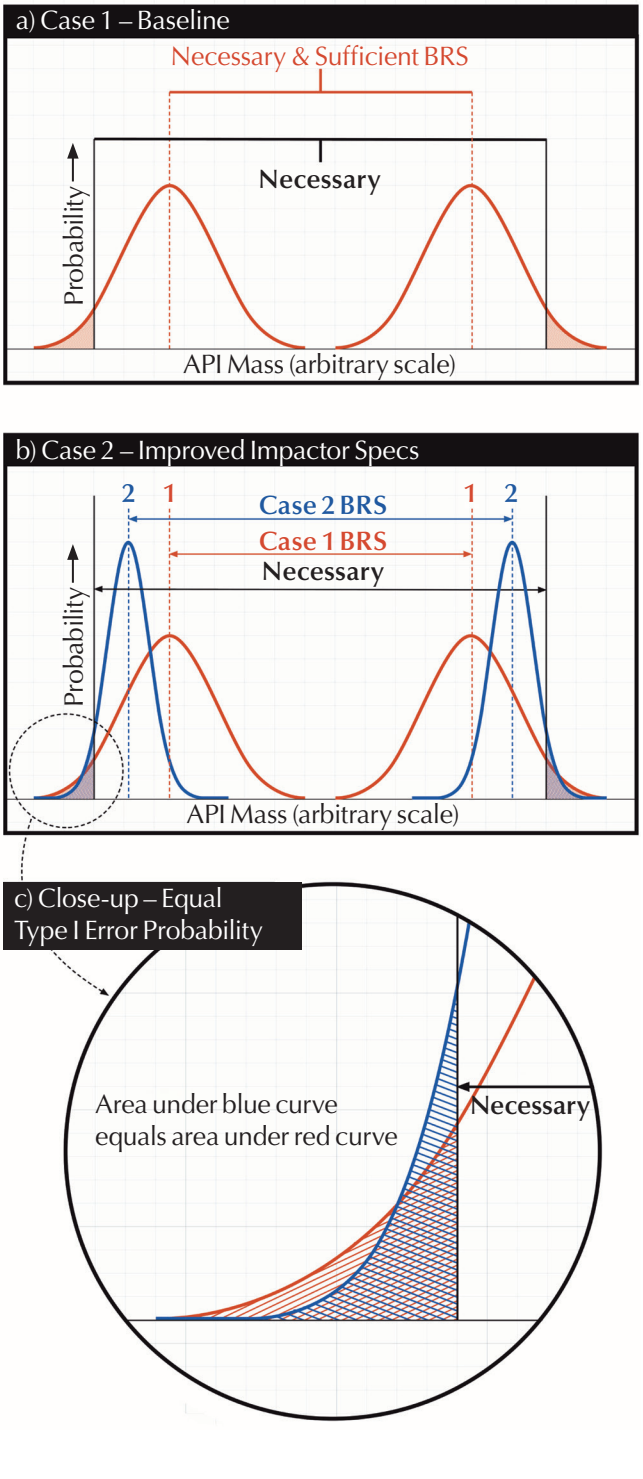
Setting a batch release specification to control Type I error probability. The width of the Gaussian curve affects the probability of a Type I error.



As in all laboratory activities, an individual measurement is influenced by one or more random analytical uncertainties, leading to the possibility of either a Type I or Type II error, as discussed by Roberts and Mitchell [6]. The focus of that article was to show that reducing the probability of Type I errors to an acceptable level decreases the range of the acceptable API mass in any individual group, compared to the nominal, necessary range of acceptable API mass. This conclusion is reiterated here in Figure 2 where the ranges of acceptable actual values of API mass are shown for the cases where "necessity" alone is satisfied and where a "necessary and sufficient" batch release specification is set in a manner that reduces the probability of a Type I error to some acceptable value, such as 5%.

Figure 3

Expanding batch release specifications by tightening D_{50} specifications and with a constant probability of Type I error. Purposeful control of impactor quality can widen batch release specifications without increasing the probability of discarding batches with adequate quality.



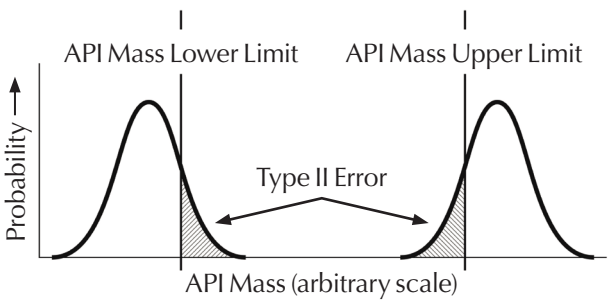
In Figure 2, the spread of the bell-shaped curves is directly related to the tightness of the specifications on the D_{50} values of the impactor stages. It is important to recognize that the tightness of the D_{50} specifications affects the breadth of the "Necessary & Sufficient" BRS shown in Figure 2. This point is reinforced by Figure 3, where a broadening of the necessary and sufficient BRS is shown to take place when the specifications on the D_{50} values of the impactor stages are tightened. This figure proceeds from a baseline case (red lines; Figure 3a), then to improved, tighter impactor specifications (blue lines, Figure 3b). This illustration then brings out the point in the inset (Figure 3c) that this broader BRS can be accomplished even without changing the probability of a Type I error (equal shaded areas of blue lines and red lines). Importantly, this review of Type I errors emphasizes that the power to control D_{50} specifications gives the user, at the time of a new drug application, a tool to use in the negotiation of batch release specifications when trying to control the probability of good product being discarded (Type I error).

Type II errors

As indicated earlier, a Type II error is a batch release test result that indicates that the test sample is within specification when, in reality, the test sample is outside the batch release test specifications (Figure 4). In Figure 4, the peaks of the bell-shaped curves indicate the true sample value, and the spread of the curves is directly related to the specifications on the D_{50} values of the impactor stages. In the context of a therapeutic drug product, this type of error is sometimes called a "con-

Figure 4

A typical Type II error. The true API mass is at the peak of the Gaussian distribution; the shaded area indicates the probability of a measurement inappropriately indicating an "in specification" result.



sumer risk" error [12] because the patient population may receive product with sub-standard effectiveness.

We now introduce the idea of one set of impactor stage specifications that is chosen to be different than the other original specifications. Considering the case where the actual API mass is the same in two samples from a given group of impactor stages, Figure 5 shows that if the API mass is more accurately known, because of tighter D_{50} specifications for the impactor (as in Case 2, blue lines), the span of the batch release specification can be greater, without increasing the probability of a Type II error (equal areas of red-shaded and blue-shaded regions). Since regulatory agencies highly value maintaining or reducing Type II error probability (maintaining/reducing consumer risk), the manufacturer should understand how the D_{50} specifications can yield expanded batch release specifications while maintaining an important regulatory goal.

The example of Figure 5 shows the "power" of the control of the D_{50} specifications. Naturally, for any given OIP, there can be one and only one BRS, namely that which results from an informed technical negotiation between the manufacturer and the regulatory agency. This process involves many factors that are outside the scope of this article. However, no matter how the agreed BRS is derived, the true sample values must satisfy the *necessary* constraint implied by the cascade impactor specifications, or the BRS cannot be met. Further, no matter how strict or relaxed the agreed BRS may be, the Type II error probability is quantifiable, depending on the impactor stage D_{50} specifications (Figure 6).

The interdependence of Type I and Type II errors

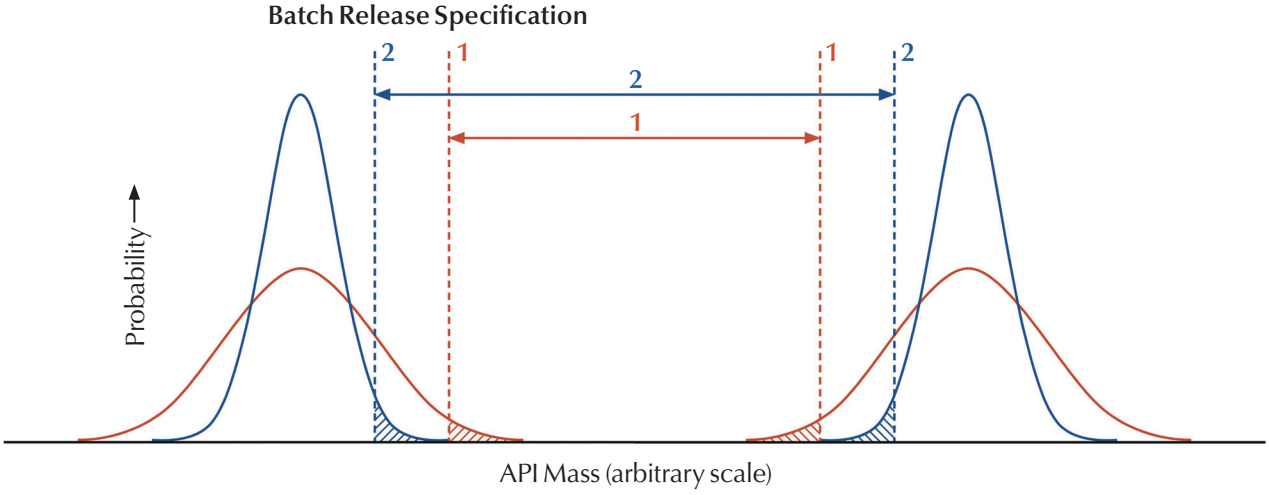
The thought process through this series of articles up to this point has followed a logic that leads from defining the *necessary* constraints, to establishing *necessary* and *sufficient* constraints related to Type I errors, to the effect of both constraints on Type II errors. We are hopeful the reader will appreciate that the thought process can proceed in any direction, depending on what one considers to be the independent and the dependent variables. For example, the more important constraint may be a limit on Type II errors, thereby limiting consumer risk. The BRS is then set by the breadth of the Gaussian curve representing the control of the D_{50} values to achieve a given Type II error probability (as in Figure 6). This control of the D_{50} values then defines the Type I probability (as illustrated by Figure 3).

There are further considerations when facing a practical example, such as depicted in Figure 1. Here, there will be one BRS for each of the four groups of impactor stages. One of these will lead to the least probability of Type II errors and may therefore be the controlling factor; however, we recognize that the final outcome could be a point of negotiation between the manufacturer and regulatory body concerned. Further, the individual BRS values among the stage groups cannot all be independent simply because mass that is not in one group must appear in some other group or groups [12]. The effect of that interdependence varies with the chosen data reduction method, an issue that is again beyond the scope of the present article.

Finally, for those desiring further independent study on the treatment of Type I and Type II error probability, an elegant description of operating characteristic curves in the context of cascade impactor testing

Figure 5

Expanding batch release specifications by modifying D_{50} specifications with no change in the liklihood of a Type II error. Purposeful control of impactor quality can widen batch release specifications without increasing the probability of releasing batches with inadequate quality.



has been presented by Christopher, et al. [section 8.4.3 of reference 13].

Quantification

The remaining challenge is, of course, the quantification of error probability for any inhalable drug product tested in any manner and with any data reduction method. The basic principles are at hand [10], but for now we will restrict ourselves to the concepts involved.

For the practicioner, in the short run, we wish to emphasize that impactor quality control means control of the stage D_{50} values themselves, not simply of the diameter of the nozzles on each impactor stage. The simplest way to remember this aspect is to think about what happens if a perfectly good OIP in terms of emitted aerosol APSD is tested with an impactor with perfectly nominal nozzle diameters on each stage, but at the wrong flow rate. In this case, all the impactor's D_{50} values are incorrect, and the mass of API in each stage is shifted, very possibly causing a good OIP batch to be discarded (a Type I error). A similar scenario can easily be imagined that leads to a Type II error. *The bottom line is that what matters are the magnitudes of the D_{50} values, not just the magnitudes of the nozzle diameters, diameters established by a method such as stage mensuration*.

Previously [6, 10] we showed that the uncertainty in the D_{50} values depends on the combination of the flow rate (Q) uncertainty with the area-mean nozzle diameter (W*) uncertainty, as follows:

$$\left(\frac{\sigma_{D50}}{D_{50}}\right)^2 = \frac{1}{4}\left[\left(\frac{\sigma_Q}{Q}\right)^2 + \left(\frac{\sigma_W}{W^*}\right)^2\right] \qquad (1)$$

We also showed that for the practical example presented in Figure 1, the uncertainty in the mass in the key stage grouping (Group 4) is given by:

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

So, the uncertainty in the measured mass fraction depends on the same parameters and does so in the same quantitative manner regardless whether one is considering Type I errors or Type II errors.

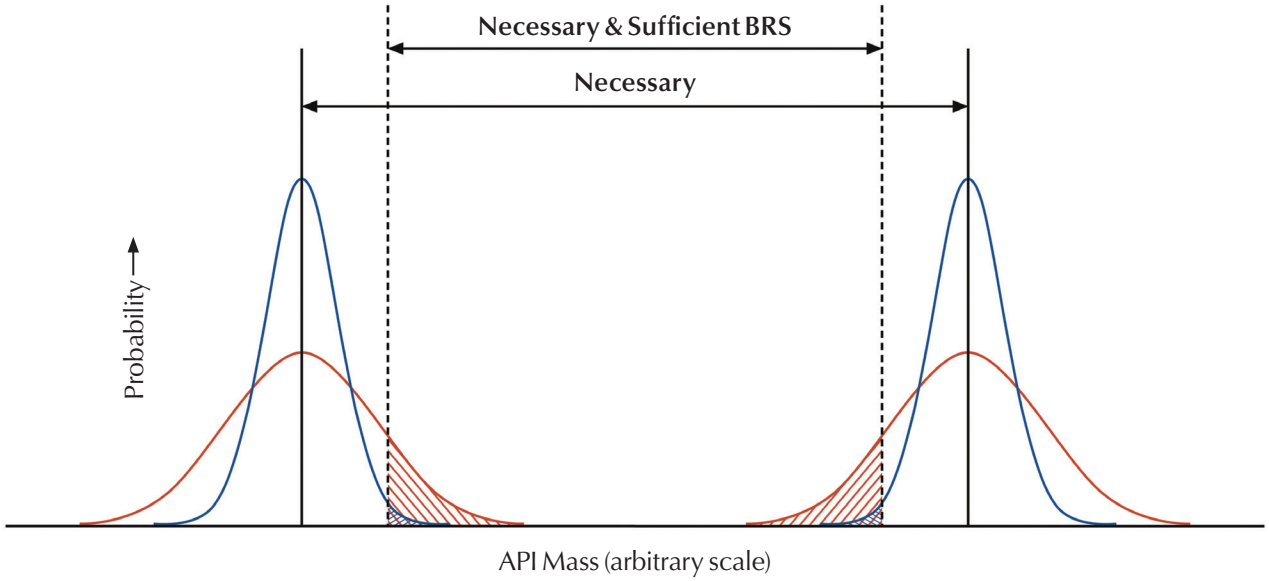
Consequently, to a first approximation, the probability of a Type II error is the same as the probability of a Type I error.

We use the phrase "to a first approximation" here to remind the reader that although the slope of the size distribution curve, $R(D_{50,5})$, appears as the same symbol when applying equation 2 to the scenario of Type I errors or Type II errors, the actual magnitude must be calculated for each case. Further, an accurate calculation of $R(D_{50,5})$ depends on the shape of the underlying mass-based aerosol APSD presented to the stage, itself. Although that result sounds complex, it is intuitively pleasing because it makes sense that the probability of violating a mass-based BRS depends on the API APSD for the inhaler-on-test.

Because of the near equality of the likelihood of Type I and Type II errors, we are able to refer the reader to our previous assessment of the relative importance of flow rate control and nozzle diameter control when aiming to control Type I error probability (see Table 5 in reference 6). Importantly, this previous summary

Figure 6

Reducing the likelihood of Type II errors by modifying D_{50} specifications with a known batch release specification. If the BRS is known, purposeful control of impactor quality can reduce the probability of releasing batches with inadequate quality.



analysis says much about the benefit of flow rate control, a factor that seems not to get much attention in typical industry methods, such as described in the pharmacopeial compendia.

Finally, we wish to leave the reader with one more thought…we go one step further and ask, "Can an individual user control the impactor nozzle diameter much better than the uncertainty arising from the manufacturer's specifications?" The manufacturer specifications result from making many impactors within an acceptable range of nozzle diameters. But individual users typically do not have a large number of impactors, and only a handful may be assigned to testing a given drug product. Further, inspection measurement tools for impactor nozzles are capable of micron-level quantification [14, 15]. In equation 1, if we substitute a nozzle diameter uncertainty of ± 3 microns instead of the manufacturer specification of ± 10 microns or more, the contribution of nozzle diameter uncertainty to the overall uncertainty in D_{50} drops by a factor of 10 or more, relative to the contribution of the flow rate uncertainty, decreasing the value of σ_{f_4} substantially, to the point that *flow rate control alone* defines and controls the impactor quality. Consequently, we pose the question: Could this goal be achieved in practice with accurate pressure drop measurements as a substitute for nozzle diameter measurement? If this scenario were to be realized, both Type I and Type II errors would be reduced, which would be a good thing for manufacturers and consumers. The added bonus for the inhaler testing community would be *that it may even be possible to eliminate annual optical inspection of nozzles, simply because the nozzle diameter uncertainty becomes unimportant in the overall D_{50} uncertainty.* An analysis of this approach awaits future investigation.

Conclusions

We have made the case in this and the preceding articles in the series [5, 6], for a method of assuring that impactor quality specifications are both necessary and sufficient, not dependent on manufacturer specifications. This method can be applied to existing drug products or inside a new drug application. The method emphasizes that the cascade impactor stage D_{50} values, at the time of testing, are the key issue, *not impactor nozzle dimensions alone and not flow rate alone*. The method is independent of manufacturer impactor nozzle specifications and introduces new possibilities for managing impactor quality. The method can be applied to any technique of impactor data reduction, such as the typical stage grouping preferred by the US FDA [11]. This approach is fully consistent with the treatment of other equipment necessary for APSD measurements, for example, the instrumentation for assaying the API(s) delivered by the product being tested. Further, we have shown that the magnitude of the Type II error probability arises as the result of a given BRS and its related necessary impactor specifications. Both can be negotiated when a manufacturer is seeking approval of a new drug application. The impactor specifications necessary for an already-established BRS can be calculated for existing drug products, and the control of D_{50} becomes a tool that the manufacturer can manage either to reduce Type I errors to the benefit of the production yield probability and/or to reduce Type II errors, thereby reducing consumer risk. Either way, we observe that this approach will be of benefit only to those who are willing to use it.

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