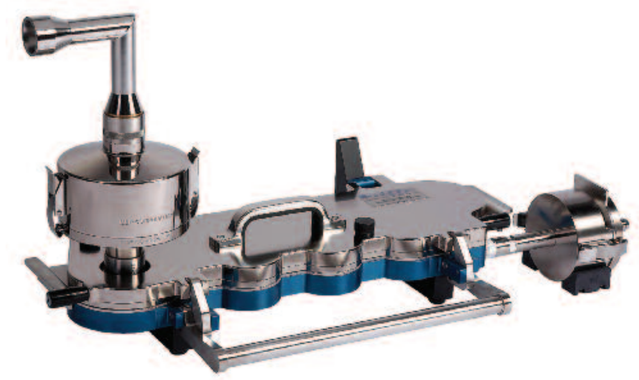
The Next Generation Impactor (NGI™)—Manufacturing Control: Part II. Collection Cups and the Critical Jet-to-Plate Distance

The second of two articles on the rationale and outcomes of manufacturing controls for the NGI



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Introduction

Various types of multi-stage cascade impactors (CI), including some repurposed from use in environmental aerosol measurements, have been for more than 30 years the mainstay for *in vitro* testing of orally inhaled products (OIPs) for aerosol aerodynamic particle size distribution (APSD) and derived parameters.[1] There are therefore several designs of CI in the pharmaceutical compendia from which the developer of an OIP may choose for inhaler evaluation.[2, 3] However, it is only since the development and commercial introduction of the Next Generation Impactor (NGI™, MSP Corporation, St. Paul, MN, US) in June 2001 that there has been an apparatus designed from first principles and purpose-built for the testing of OIPs.[4]

In part I of this two-part article series, we reviewed the control associated with the manufacture of each NGI nozzle piece because, for cascade impactors, nozzle dimensions are the most important parameters to control.[5] The nozzle *effective diameter* for each stage is directly related to the effective cut-off diameter (ECD) of the given stage and therefore influences both the accuracy and precision to which an APSD may be determined.[6] In this article, we describe control of the more subtle, but often equally important matter: the *collection surface profile* that is presented to the incoming aerosol particle—both its dimensions and its position relative to the nozzles.

Describing the collection surface

The condition of the collection surface must be understood microscopically in terms of its surface roughness and macroscopically by its position relative to the plane where the air flow exits the nozzles at each stage. In the NGI, the collection surface is the floor of a cup. Particles approaching the cup surface will permanently leave the diverging air streamlines beneath each nozzle if these particles are large enough to impact on the surface. The user's need to coat these cups in a repeatable manner demands a highly repeatable and flat surface. At the same time, the separation from the nozzle exit plane to the collection surface influences the efficiency with which particles of a given size will reach the collection surface.[7] It follows that if the ultimate goal of the impactor designer is to reduce both impactor-to-impactor and test-to-test variability, it is important to impose strict control, not only on nozzle diameter, but also on the separation distance between the nozzle exit plane and the plane defining the cup floor. Consequently, strict control is required on the cup depth and on all dimensions that affect this separation distance.

Theoretical basis

Marple first articulated quantitatively the importance of the distance from the nozzle exit plane to the collection surface in the proper operation of a cascade impactor.[7] Rader and Marple later refined the calculations to include particle collection by interception and to include more realistic particle-fluid drag forces in excess of that predicted by Stokes Law.[8] These theoretical considerations revealed that a key parameter in the size-fractionating ability of an impactor stage is the ratio of the distance from the nozzle exit plane, commonly given the symbol S, to the nozzle diameter, commonly given the symbol W (Figure 1).

In Figure 1, we show, schematically, air flowing through a group of nozzles in a manner that illustrates the basic geometric configuration for each individual stage of the NGI. Early theoretical descriptions considered each nozzle to operate independently, and only later did a definition of adequate nozzle spacing appear.[9] The NGI design does follow these *independent nozzle* guidelines,[1] and therefore, for the practicing cascade impactor user, when the ratio S/W is 1-5, for all intents and purposes the particle collection efficiency curve is nearly constant (Figure 2). Still, when this ratio exceeds 10, the collection efficiency quickly falls to zero (indicating ineffective size-separation capability), and when the ratio is 1 or less than 1, the particle collection efficiency also decreases substantially (indicating enhanced sensitivity of the size-separation process to the magnitude of S/W).

In the NGI design, we were able to achieve the ratio of S/W in the ideal range of 1-5, except for the micro-orifice collector (MOC)—the S/W is approximately 1.1 for stage 1; 2-5 for stages 2 to 7; and approximately 8 for the MOC. However, the *manufacturing challenge* is achieving this range all the time, given that all NGI cups, cup trays and NGIs must be interchangeable. That is, it would be unacceptable to constrain the user to place and keep a particular NGI cup at a particular stage, with a particular cup tray, on a particular NGI. Such a restriction would defeat the *workstation* nature of the NGI that was intended from its inception, wherein the user can own any number of cups and cup trays and any number of NGIs and quickly run test after test without worrying about the origin of each component.

Figure 1

Definition of the jet-to-plate parameters for cascade impaction

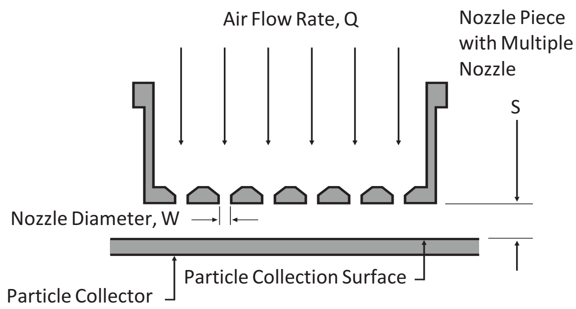
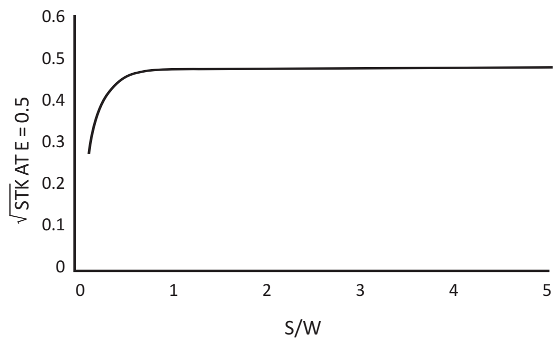


Figure 2

Variation in the square root of the Stokes Number (STK) defining the effective cut-off diameter (ECD) of a given impactor stage with S/W; (simplified from Figure 4-16 of Marple[7])



Analysis of the ratio S/W

A claim for interchangeabilty of parts demands that we consider the *probability* that any random set of parts maintains the design intent. In the NGI, the S/W ratio is a result of several independent machined parts, some of which have more than one independent critical dimension. A cross-section of the NGI, taken through the midplane of one of the small cups (stages 2 to 7), shows that the dimensions of the lid, the seal body, the bottom frame, the cup lip, the cup depth and the cup tray all have impact (Figure 3). The two-dimensional analysis depicted in Figure 3 is sufficient so long as the lid and bottom frame of the NGI are flat and parallel when the NGI is closed.

Figure 4 gives an in-depth look at the design. Here, the independent variables are shown that define S from an analysis based on the front hinge pins and from an analysis based on the rear hinge pins. The two inset sections within Figure 4 show, in detail, where the seal body O-rings contact the cup lip and the NGI lid, and where the nozzle piece itself hangs on the seal body. The magnitudes of the critical dimensions, defined in these insets, apply whether one is considering the front hinge pins or the rear hinge pins as the basis of the analysis.

Choosing proper *nominal* values of each independent variable to achieve an S/W value for each stage within the ideal range was a significant challenge in the design of the NGI. Proper nominal design dimensions are necessary *but insufficient* for ensuring proper S/W values for all combinations of cups, cup trays and NGIs. This is because each machined part cannot be perfectly made to its nominal dimension and, as a consequence, has its own dimensional tolerance. *Tolerance buildup* is a practical form of *propagation of error*.[10] In the case of the NGI, tolerance buildup must be considered to control the overall uncertainty in the magnitude of S, as shown in Figure 4.

In setting design parameters and their related uncertainties for the NGI, we chose to give as much tolerance range as we could to the cup depth, the cup lip thickness and the cup tray thickness, after considering which parts could be made more easily than others. We chose the cup depth tolerance to be +/- 0.10 mm (nominal 14.625 mm) and the cup lip thickness tolerance and the cup tray thickness tolerance to be +/- 0.05 mm (nominal 0.81 mm and 3.00 mm, respectively). The nozzle diameter ranges were chosen separately to achieve the desired ECD values, as described previously.[1]

The analysis shown in Figure 4 yields a quantitative value for the uncertainty in S. The uncertainty in S/W can be calculated from the uncertainty in S and the uncertainty in W as follows:

$$\sigma^2_{s/w} = \frac{\sigma^2_s}{W^2} + \frac{S^2\sigma^2_w}{W^4} = \frac{1}{W^2}\left(\sigma^2_s + \frac{S^2\sigma^2_w}{W^2}\right) \qquad [1]$$

Since S/W is in the range of 1-5, equation 1 calls to our attention that the uncertainty in the nozzle diameters is (perhaps surprisingly) *amplified* when one wishes to calculate the uncertainty in the ratio S/W [for example, if S/W is nominally 3.0, the sigma-W term in equation 1 is multiplied by 9].

Table 1 gives the calculated uncertainty in S, the given uncertainty in W, the nominal value of S/W and the resulting uncertainty in S/W for the NGI. The specification ranges that we chose for S/W (right-most column), allow a minimum of 2 sigma (95% confidence), with the exception of stage 7, where the specification range is 1.5 sigma (87% confidence; there are various reasons for this choice, beyond the scope of this article, but it was chosen mainly so that the S/W value does not exceed 6).

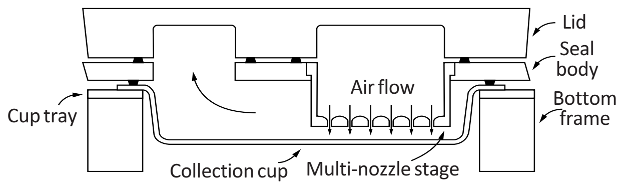
The controlled dimensions of each part influencing the S/W value for each NGI is indicated in each certificate of conformance for each NGI. Furthermore, in the NGI, since the nozzle pieces are fixed in place by a metal-to-metal interference fit, not adjustable or removable by the practicing technician, the S/W values can be confidently known to be within the specified ranges after many, many years of practical use.

Cup depth: A major issue

We will focus the rest of our discussion on the NGI cup dimensions, because users expect, as a quality attribute, not only the correct cup depth but also several unspoken characteristics that relate to its overall performance in use. One of these important attributes, not thus far described in connection with the theory of cascade impaction, is cup flatness. This issue is critical for the NGI user because cups routinely need to be coated to eliminate particle bounce.[11, 12] A cup with an uneven collection surface will either puddle the coating fluid into a corner or pool it in several locations, leaving uncoated surfaces exposed. For this reason, we allow no points on the floor of the cup to be out of the specification for depth (we check 9 points for a small cup and 17 for a large cup; Figures 5 and 6).

Figure 3

Cross-section of the NGI showing parts influencing the jet-to-plate distance S



This multipoint inspection ensures cup flatness, at the same time ensuring proper cup depth across the critical region where particles are deposited. The thoughtful user knows that it is insufficient for the cup to satisfy the depth specification *on average*. That is because a cup could, in principle, have an *in spec* average depth *but at the same time have every single measured depth out of specification.*

Furthermore, the cup depth must be determined relative to the flat plane of the cup lip. For that reason, we define the location of the cup lip first so that the *depth* dimension at each point on the floor of the cup has a defined meaning.

It is worthwhile noting at this juncture that the first batch of NGI cups were machined to a visibly smooth surface (Figure 7). We received almost immediate user feedback to the effect that an untreated, smooth, stainless steel surface was too difficult to wet with coating fluids that are widely used. A surface roughening method at the microscopic scale was needed that, at the same time, did not affect particle collection, which would happen if the flow boundary layer were altered at the point of impaction under each nozzle. The resolution of this surface wetting problem was to finish the surface by means of a glass bead attrition process, resulting in a surface roughness factor of 0.5-2 micron (Figure 8). This finish is rough enough for typical coating solutions to spread evenly, but is not so

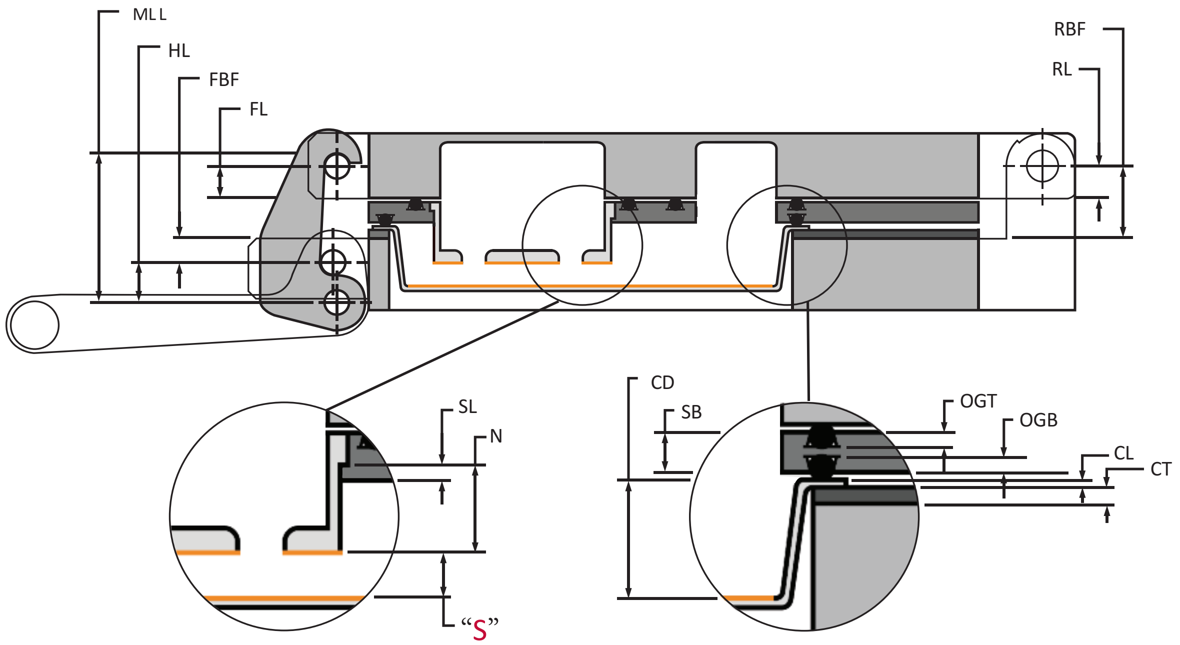
Table 1

Uncertainty in Jet-to-Plate Distance and Resulting Practical Specification

Stage Number	Sigma S (mm)	Sigma W (mm)	Nominal S/W	Sigma (S/W)	Specification Range
1	0.154	0.05	1.049	0.01191	± 0.1
2	0.162	0.04	2.001	0.03701	± 0.2
3	0.162	0.02	3.000	0.07907	± 0.3
4	0.162	0.01	3.000	0.13651	± 0.4
5	0.162	0.01	3.000	0.36315	± 0.8
6	0.162	0.01	3.099	0.51070	± 1.0
7	0.162	0.01	4.854	0.82104	± 1.2

Figure 4

Analysis for jet-to-plate distance S and resulting uncertainty



This figure displays the individual dimensions that together define the distance "S" from the nozzle exit plane to the cup collection surface. The value of "S" can be calculated from the rear hinge pins or from the front hinge pins.

Rear hinge analysis:

$$S = \frac{1}{2}(RBF - RL - SB - CT - CL - OGB + OGT) + CD + SL - N$$

Front hinge analysis:

$$S = \frac{1}{2}(MLL - FL - HL - FBF - SB - CT - CL - OGB + OGT) + CD + SL - N$$

The uncertainty in "S" can then be calculated as follows:

Rear hinge analysis:

$$\sigma_S^2 = \frac{1}{4}(\sigma_{RBF}^2 + \sigma_{RL}^2 + \sigma_{SB}^2 + \sigma_{CT}^2 + \sigma_{CL}^2 + \sigma_{OGB}^2 + \sigma_{OGT}^2) + \sigma_{CD}^2 + \sigma_{SL}^2 + \sigma_N^2$$

Front hinge analysis:

$$\sigma_S^2 = \frac{1}{4}(\sigma_{MLL}^2 + \sigma_{FL}^2 + \sigma_{HL}^2 + \sigma_{FBF}^2 + \sigma_{SB}^2 + \sigma_{CT}^2 + \sigma_{CL}^2 + \sigma_{OGB}^2 + \sigma_{OGT}^2) + \sigma_{CD}^2 + \sigma_{SL}^2 + \sigma_N^2$$

Symbol	Component, rear hinge
RL	Rear hinge pin location, lid
RBF	Rear hinge pin location, bottom frame

Symbol	Component, front hinge
FL	Front hinge pin location, lid
MLL	Main latch link (center-to-center)
HL	Handle link (center-to-center vertical separation at closure)
FBF	Front hinge pin location, bottom frame

Symbol	Common components
SB	Seal body thickness
CT	Cup tray thickness
CL	Cup lip thickness
OGT	Depth of O-ring groove on top of seal body
OGB	Depth of O-ring groove on bottom of seal body
CD	Cup depth
SL	Stop lip
N	Nozzle piece protrusion

Figure 5

Inspection points on the small NGI cup for determining lip and surface flatness and cup depth

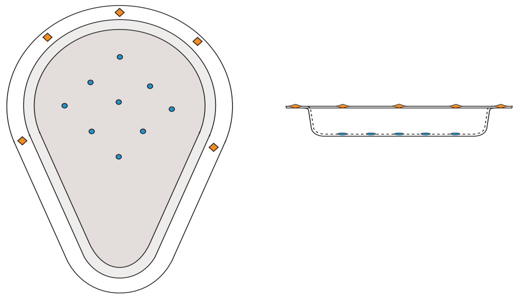
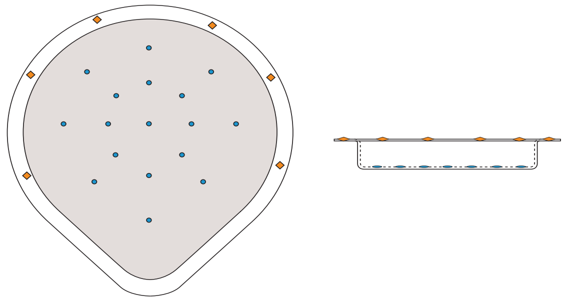


Figure 6

Inspection points on the large NGI cup for determining lip and surface flatness and cup depth



rough as to adversely affect particle deposition, even at stage 7 of the NGI where the air flow boundary layer is only about 200 microns in height.

Surprisingly, in the surface roughening work, we found that finished cups were, on average, about 0.08 mm more shallow than raw cups—that is, the depth of the cup actually changed during surface roughening (Figure 9). This change can be accommodated by adjusting the depth of the raw cup; but we have also been learning over the years how to minimize this effect. Because of these efforts, we are now beginning to study a statistical sampling method for inspecting NGI cups and hope to satisfy ISO 2859 requirements in the near future.

Cup leakage

As impossible as it first seemed to us, even when the cups are manufactured carefully, achieving the correct cup depth and lip thickness, we have discovered that cups can leak with a minor, normally unobservable slit at the point that the lip curls down to the sidewall of the cup, even though the cups are made of 316 stainless steel (Figure 10; the dashed red line emphasizes the crack line on a faulty cup). This type of flaw can result from over-stretching the material with insufficient lubrication in the deep-draw process. We have manufactured approximately 20,000 cups. Yet it is unacceptable to our users that even one cup like that illustrated in Figure 10 would be shipped to them. We therefore test all cups for leaks. Because hairline flaws can be surprisingly difficult to see, we also suggest users *not* alter the cups, such as by adding their own serial number, because it is possible to inadvertently penetrate the wall of the cup with engraving tools, thereby inadvertently introducing a leak.

Conclusions

The unique nature of the development of the NGI, as the first CI that was developed for the specific purpose of the laboratory assessment of aerosols from OIPs, provided opportunities from its inception to pay attention to and resolve issues such as the manufacturing stability of critical components of the NGI. This approach was an essential part of meeting the goal of achieving consistent component manufacturing. From the outset, we regarded this practice as key to meeting the high quality demands of industrial users operating in a highly regulated environment. The process of achieving a stable design necessitated resolving several design-for-manufacturing problems relating to critical components in a satisfactory manner for users. In Part I of these articles, we described how we control nozzle dimensions to a tight tolerance and how the concept of effective diameter and its associated in-use margin establishes a quantitative measure of the quality of both new and used NGIs. This concept did not increase the burden on users because periodic stage mensuration was already part of the existing performance verification process.

In Part II, we have addressed the manufacturing control necessary to maintain the proper nozzle separation distance from the cup collection surface. Control of this dis-

Figure 7

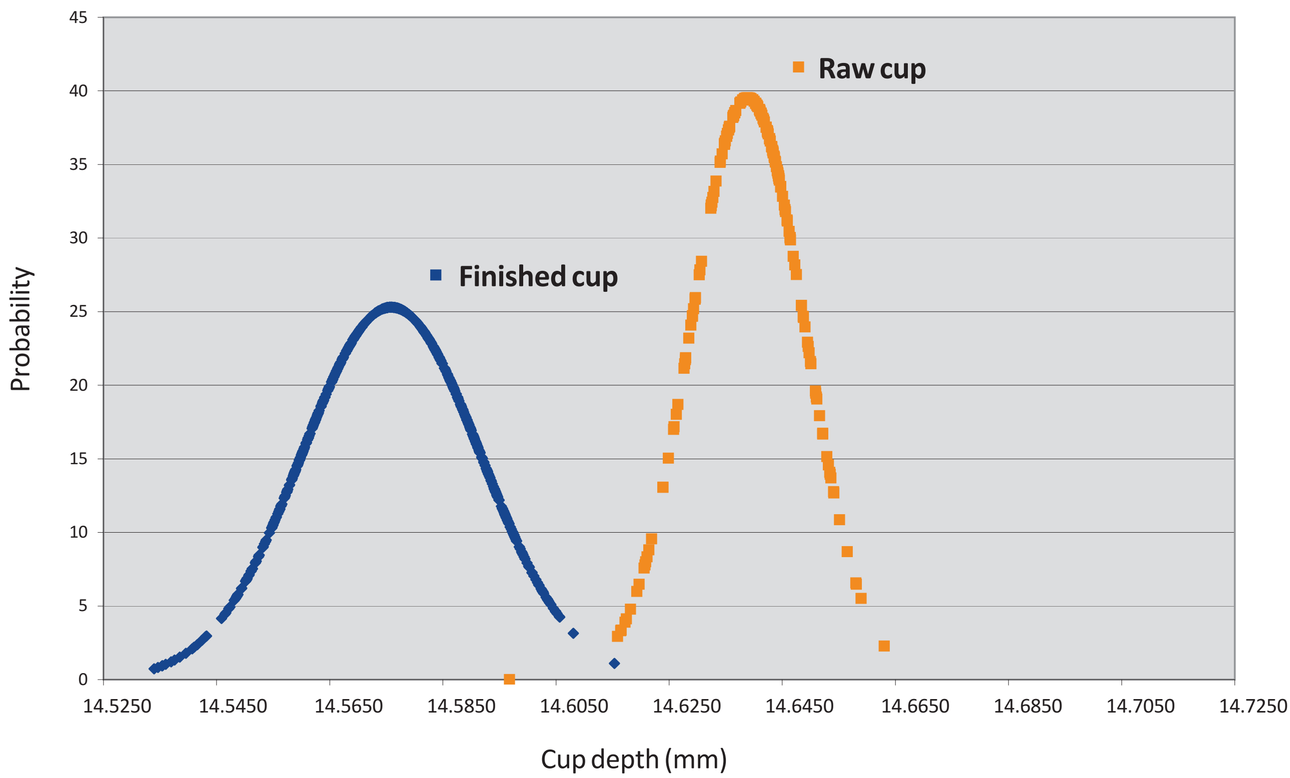
Machined cups in the first approximately 25 NGIs

Figure 8

Today's flat, surface-roughened, 316 stainless steel cups

Figure 9

Change in cup depth as a result of surface roughening



tance requires a proper understanding of tolerance buildup, which derives from the requirement that all NGI parts be interchangeable. For coating purposes, a proper cup collection surface must also be flat and wettable. Consequently, we have had to address micron-level control of surface roughness while maintaining a proper cup depth and flatness. In doing so, we have achieved the manufacture of all NGIs such that apparatuses are not only fit-for-purpose at the time of acquisition, but can regularly be verified as remaining so, by means of optical inspection/mensuration methods that are in widespread use. The manufacturing controls we have described in these articles should therefore reassure users that their NGIs will continue to serve their intended purposes for many years to come.

References

1. Mitchell, J. P., M. W. Nagel, "Cascade Impactors for the Size Characterization of Aerosols from Medical Inhalers: Their Uses and Limitations," J. Aerosol Med., 16, 341-77 (2003).

2. European Directorate for Quality in Medicines and Healthcare (EDQM), European Pharmacopoeia 8.0, Monograph 2.9.18, "Preparation for Inhalations: Aerodynamic Assessment of Fine Particles," Strasburg, France, EDQM, January 2014.

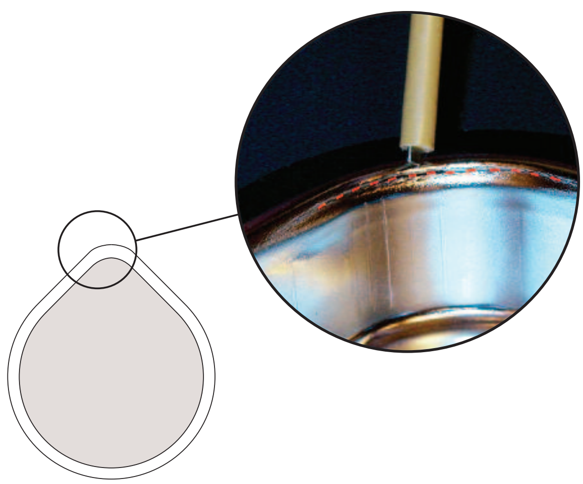
3. U.S. Pharmacopeial Convention, United States Pharmacopeia 39/National Formulary 34, Chapter 601, "Aerosols, Nasal Sprays, Metered-Dose Inhalers, and Dry-Powder Inhalers," Rockville, MD (2016).

4. Marple, V. A., D. L. Roberts, F. J. Romay, N. C. Miller, K. G. Truman, M. Van Oort, B. Olsson, M. J. Holroyd, J. P. Mitchell, D. Hochrainer, "Next Generation Pharmaceutical Impactor—Part I: Design," J. Aerosol Med., 16, 283-99 (2003).

5. Roberts, D. L., J. P. Mitchell, "The Next Generation Impactor (NGI™)—Manufacturing Control: Part I. Nozzles," Inhalation, 10, 12-9 (April 2016).

Figure 10

Hairline tear near cup lip (red dashed line added for clarity)



6. Roberts, D. L., "Theory of Multi-Nozzle Impactor Stages and the Interpretation of Stage Mensuration Data," Aerosol Sci. Tech., 43, 1119-29 (2009).

7. Marple, V. A., "A Fundamental Study of Inertial Impactors," PhD Thesis, Mechanical Engineering Department, University of Minnesota (1970).

8. Rader, D. J., V. A. Marple, "Effect of Ultra-Stokesian Drag and Particle Interception on Impaction Characteristics," Aero. Sci. Tech., 4, 141-56 (1985).

9. Fang, C. P., V. A. Marple, K. L. Rubow, "Influence of Cross-Flow on Particle Collection Characteristics of Multi-Nozzle Impactors," J. Aerosol. Sci., 22, 403-15 (1991).

10. Bevington, P. R., D. K. Robinson, " Data Reduction and Error Analysis for the Physical Sciences," 3rd Edition, McGraw-Hill, New York, NY (2003).

11. Kamiya, A., M. Sakagami, M. Hindle, P. R. Byron, "Aerodynamic Sizing of Metered Dose Inhalers: An Evaluation of the Andersen and Next Generation Pharmaceutical Impactors and Their USP Methods," J. Pharm. Sci., 93(7), 1828-37 (2004).

12. Mitchell, J. P., "Practices of Coating Collection Surfaces of Cascade Impactors," Drug Delivery to the Lungs XIV, The Aerosol Society, December 11-12, 2003, pg. 75-79.

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