Inspecting used impactors—Practice and principles

Being confident about quantifying the imperfect

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Cascade impactors are the backbone of quality control for inhalable drug products. Consequently, ensuring that used impactors are suitable for continued use is a basic need for developers and manufacturers of inhalable drug products. Industrial standards, such as the United States Pharmacopeia or the European Pharmacopoeia, describe periodic optical inspection of the nozzles of each stage of an impactor as the means of ensuring that the impactor is suitable for continued use. The notion of "periodic" is left to the user to validate, but it is most common for users to seek independent, third-party inspection of impactors every six months or 12 months.

Most of the available literature on inspecting impactors focuses on new impactors. For example, Chambers et al.[1] have described available optical inspection tools for measuring the diameter of the nozzles in cascade impactors, particularly as applied to representative new impactor nozzles. Mitchell[2] summarized some of the existing practices for determining whether used impactors are suitable for continued use, including leak checking, cleaning and optical inspection, but there is little evaluation of preferred methods.

In used impactors, more questions arise during inspection than for new impactors. For example, used impactor nozzles have more irregular edges than do new impactor nozzles. Consequently, the focus of an optical inspection machine at the nozzle exit plane can become less defined, sometimes as a result of corrosion (mostly of the aluminum impactors) or because of inappropriate cleaning attempts. In addition, nozzles are three-dimensional and from time to time, extraneous debris can appear inside the nozzle of a used impactor. Questions arise about when and if and how to clean nozzles. Overall, the assessment of suitability of used impactors, therefore, requires attention to a number of factors not present with new impactors.

This article describes ways to approach these issues and suggests practical methods for inspecting used impactors in a manner that accounts for their various non-ideal conditions.

Shipping and getting started

Surprisingly, users ship impactors for inspection using a wide range of physical packaging arrangements, which are not always favorable. Frequently, used NGIs are shipped without cups that could protect the nozzle pieces. Used Andersen impactors are often shipped with their nozzle pieces placed separately in the packaging rather than being stacked and clamped together. Transporting a completely assembled impactor is the safest arrangement because the nozzles are protected from damage. Figures 1a and 1b show sample best practices for shipping the NGI and the Andersen impactor.

When a used impactor arrives at its destination, after visual inspection for dents, scratches and debris, the first question that must be determined is the degree of

cleaning the impactor stages should undergo—if any—before optical inspection. Impactor users need to know if their routine laboratory work practices keep their impactors suitable for use during the six months or 12 months between inspections. Obviously, if the optical inspector were to clean the nozzles of the impactor stages before inspecting, the user cannot answer this key question. Therefore, it is important *not* to clean the impactor before inspection, but rather to lightly blow the impactor stages with clean compressed air to remove dust particles or packaging debris that may have attached themselves to the impactor during transit. This practice gives the optical inspector the ability to tell the user the information he or she needs, namely the "as found" results, without surprises from spurious dust, hair or packaging materials.

Optical inspection

In concept, the optical inspection, sometimes called "mensuration," determines if the nozzles are the proper diameter, as in USP section 601 and EP section 2.9.18. In Figures 2a, 2b and 2c, we see three types of nozzles—a perfect nozzle, a typical nozzle and a rare and difficult nozzle. Inspection methods for used impactors must anticipate all types, not just the clean, round nozzles typical of new impactors.

Figure 2c emphasizes not simply the potential for a nozzle to be dirty. Rather, this figure shows the three-dimensional aspect of impactor nozzles, which are typically as deep, in the direction of air flow, as the nozzle exit-plane diameter. In Figure 2c, the focus is on the nozzle exit plane and the out-of-focus contaminants are upstream of the nozzle exit plane.

Figure 1

Proper packaging for shipping used impactors

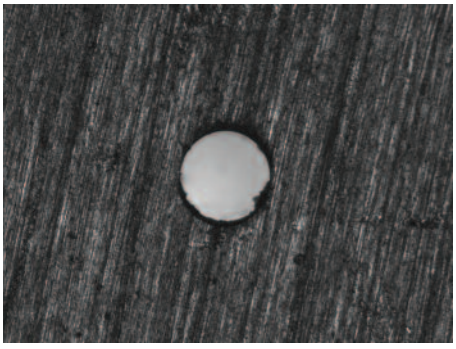
a) NGI

b) Andersen impactor

Figure 2

Examples of nozzles found in used impactors

a) Clean, round nozzle



b) Typical, used nozzle

c) Nozzle with contaminants at the exit plane and the interior of the nozzle

Because of the various imperfections encountered in the inspection of used impactors, it is critical that the optical inspection eliminate human focus and other judgment factors. Repeatability, especially in the presence of human bias, is a necessary but insufficient requirement for optical inspection. Optical inspections must also be accurate. For this reason, optical inspections should be conducted with equipment that has an automated, operator-independent means of defining the edge of the nozzle and of determining the lighted area of the nozzle. The equipment used at MSP Corporation is the Mitutoyo QV404 optical inspection tool, which is known to have one-micron or smaller repeatability and accuracy for measuring nozzles of the most common inhaler testing impactors.[3] For the NGI and the Andersen impactor, the nozzle locations have been programmed for automatic operation. More importantly, the system has been qualified with proper settings for focus, brightness and the intensity definition of an edge pixel, with NIST-traceable reticles, eliminating operator biases.

Handling optical data

Optical systems like the Mitutoyo report two diameters from two fundamentally different means of looking at the nozzles. In one means of assessing the lighted pixels, the Mitutoyo system determines the Area-Based Diameter (ABD) by counting the number of lighted pixels. The ABD is calculated from the total area of lighted pixels by the equation:

$$ABD = \left(\frac{4 * area}{\pi}\right)^{1/2}$$

Essentially, the ABD is the diameter of a perfect circle that would have the same area of lighted pixels as the nozzle being examined.

The Mitutoyo system also reports the Edge-Contrast Diameter or ECD. The edge is located first by finding all pixel pairs that consist of a lighted pixel and an unlighted pixel oriented with the lighted pixel toward the inside of the circle. The Mitutoyo software then calculates the length of a contiguous line that connects the intersections of these pixel pairs. The length of this line is the circumference of the edge of the nozzle, which has been given the symbol "C." The ECD is calculated from the formula:

$$ECD = \frac{C}{\pi}$$

Essentially, the ECD is the diameter of a perfect circle that has the same circumference as the nozzle being examined.

For various reasons of imperfection in the nozzles, the ABD and the ECD are not equal in used impactors (nor are these measures precisely the same for new impactor nozzles, providing a measure of roundness). Both diameters are important to the aerodynamic performance of the nozzle. Roberts[4] has shown that the most meaningful nozzle diameter is the "effective diameter" of each nozzle (and of the stage) calculated by the simple formula:

$$D_{eff} = (ABD)^{2/3} \bullet (ECD)^{1/3}$$

A rational acceptance criterion for used impactors is therefore whether the effective diameter of a stage is in the range of nozzle diameters allowed by the USP and the EP.[4]

What if some nozzles need cleaning?

There are times when a stage of an impactor has little or no "in-use" margin [that is, it is right on the edge of the allowed range of effective diameter]. It is important to seek the user's input at this point, because it is important not to change the impactor without the user's consent. It is ideal to tell the user exactly which nozzles need cleaning, but in some cases, the entire stage needs to be thoroughly cleaned. Suitable cleaning methods include ultrasonification and manual cleaning with small dental brushes (e.g. Kleen Teeth; http://www.kleen-teeth.com/mycategory.php?do=cat&cname=End-Tufted_Brushes.html) or pins that are smaller than the nozzle diameter.

A typical biodegradable, solvent-based cleaner can be useful for the tough cases where material is not easily dislodged (e.g. Krud Kutter; www.krudkutter.com). Soaking the nozzles in this type of solvent is a benign cleaning method that does not introduce defects in the edges of the nozzles.

If one or more nozzles need cleaning, the "as left" data will differ from the "as found" data. The nature of the change in the data can be instructive to the user as to steps to take to improve his or her own methods of keeping nozzles clean between periodic inspections.

Flow resistance

As an additional means of finding unexpected, non-ideal conditions, it is valuable to examine the flow resistance of each impactor stage. Measuring flow resistance requires measuring the pressure drop at a given, controlled flow rate. Milhomme et al.[5] and Shelton et al.[6] have described this method of examining impactor nozzles. Clean, perfect nozzles have a flow resistance somewhat greater than that predicted by the Bernoulli relationship:

$$\Delta P = \frac{1}{2} \rho V^2$$

The more imperfect the nozzles are, the greater the deviation from this simple relationship. In particular, defects that are *not* in the nozzle exit plane will cause greater deviations since the optical systems focus on the nozzle

exit plane. The type of imperfection shown in Figure 2c is particularly difficult to find because much of the contamination is not in the plane of optical focus. Flow resistance measurements assist the inspector in detecting this kind of contamination.

Examples of impactor histories

Little data have been presented in the open literature on the experience of inspecting used impactors. Two examples are presented here to indicate the types of behavior that can be observed, if the approach described above is implemented by the inspector.

In the first example, we follow the time history of a particular NGI stage 6. The impactor stage starts new with the effective diameter exactly nominal (0.323 mm; Tables 1 and 2). At its first inspection, the nozzles had become reduced by some form of contaminant build up.

It was found that the practices of the user were contaminating the nozzles with a material that was not easy to remove. Whereas the nozzles on stage 6 were relatively nominal at the outset, when the impactor came for its first inspection, the average nozzle diameter was, in fact, too small to be within acceptable limits. Upon ultrasonic cleaning, the nozzles were opened to bring the average diameter back to 0.318 mm. This experience has been repeating itself. The user has been informed and is not able to identify anything specific that he can change to keep the nozzles more open. One option for this user is more frequent inspection and cleaning. However, during the most recent cleaning, the solvent soaking method and ultrasonification were used and these steps resulted in a cleaner 'as left' condition. This user is repeatedly coached about keeping the nozzles within specifications because it can take time and effort to reach a satisfactory, long-term performance.

In a second example, even with the best of information, users do not necessarily take appropriate steps. In this example of a stage 4 of an NGI, the nozzles start rather close to the nominal size but then consistently and slowly decrease in size (Tables 3 and 4). A prudent step would have been to clean the nozzles after the 'as found' data in October 2010 showed that the nozzles were near the lower limit of 1.197 mm. The user appreciated the warning and chose to do the cleaning himself. It is hoped that when the impactor returns for inspection in late 2011, the nozzles are in satisfactory condition.

A few simple rules

Observing a few simple rules in the periodic inspection of used impactors can result in a high degree of confidence when the impactor is placed back into service:

1) Use an optical inspection tool whose focus, calibration and edge-definition are independent of human bias.

Table 1

History of an NGI stage 6, NGI-0098

	New	Apr 2010	Nov 2010	Jun 2011
As found	N/A	0.311 mm	0.312 mm	0.311 mm
As left	0.323 mm	0.318 mm	0.318 mm	0.321 mm

Table 2

Distribution of nozzle sizes for NGI stage 6 (as left), NGI-0098

Size of nozzles	New	Apr 2010	Nov 2010	Jun 2011
Smaller than 0.313 mm	3	17	10	2
0.313 mm to 0.320 mm	77	260	272	91
0.321 mm to 0.325 mm	187	119	114	303
0.326 mm to 0.333 mm	129	0	0	0
Larger than 0.333 mm	0	0	0	0
Total	**396**	**396**	**396**	**396**

Table 3

History of an NGI stage 4, NGI-0407

	New	Sep 2008	Sep 2009	Oct 2010
As found	N/A	1.204 mm	1.201 mm	1.198 mm
As feft	1.208 mm	1.204 mm	1.201 mm	1.198 mm

Table 4

Distribution of nozzle sizes for NGI Stage 4 (as left), NGI-0407

Size of nozzles	New	Sep 2008	Sep 2009	Oct 2010
Smaller than 1.197 mm	0	0	3	14
1.197 mm to 1.204 mm	0	35	46	36
1.205 mm to 1.209 mm	50	16	3	2
1.210 mm to 1.217 mm	2	1	0	0
Larger than 1.217 mm	0	0	0	0
Total	**52**	**52**	**52**	**52**

2) Determine the effective diameter, consisting of the edge-based diameter and the area-based diameter, when assessing suitable aerodynamic performance.

3) Determine the 'as-found' condition of the impactor nozzles and, if cleaning is required, the 'as-left' condition, enabling the user to assess the effectiveness of his or her routine impactor maintenance practices.

4) Measure flow resistance to determine if material outside of the optical focus plane is affecting nozzle performance.

By following these rules, which are based on the fundamentals of the impactor performance, one can proceed with confidence.

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