Statistical Analysis of Andersen Cascade Impaction Mensuration Data

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Introduction

There has been a lot of interest and debate recently in the pharmaceutical industry concerning the causes of variability in cascade impaction measurements and developing approaches to reduce this variability (1,2,3). There are many factors which can influence cascade impaction results and this publication demonstrates that if Andersen Cascade Impactors (ACIs) are maintained and cleaned in a controlled way then there is negligible trending in the critical parameters of the instruments.

The USP defines the critical parameters for the manufacturer's specification of ACI stages (Equipment 1 in Section <601>) as described in Table 1.

Stage number	Number of Jets	Nozzle Diameter (mm)	Tolerance (mm)	Tolerance (%)
0	96	2.550	± 0.025	±1.0
1	96	1.890	± 0.025	±1.3
2	400	0.914	± 0.0127	±1.4
3	400	0.711	± 0.0127	±1.8
4	400	0.533	± 0.0127	±2.4
5	400	0.343	± 0.0127	±3.7
6	400	0.254	± 0.0127	±5.0
7	201	0.254	± 0.0127	±5.0

Table 1. Manufacturer's specification for the ACI Equipment.

Pharmaceutical companies mensurate ACIs on a regular basis (4) as recommended in USP guidance. 3M Healthcare Ltd has mensurated stainless steel ACIs on the Loughborough site on an annual basis over the past 5 years at Copley Scientific Ltd using a Mitutoyo QV404 Pro Vision Inspection System (VIS). This publication includes mensuration data of individual stages and induction ports over this period.

Results and Discussion

The trend graph for mean hole diameter for each stage (expressed as a percentage variation from nominal hole diameter) for all ACIs demonstrates that every stage on every ACI is remaining within the USP's manufacturer's specifications (see Figure 1). The trending is slightly larger for stages 0 and 1, however this does not represent an analytically significant factor.

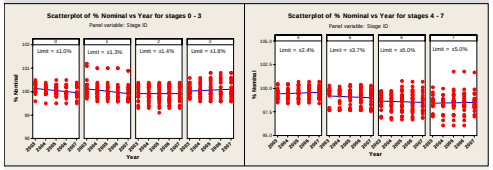

Figure 1. Scatterplot of stage diameters expressed as a percentage of the nominal diameter versus year for each ACI stage.

It is interesting to note in Figure 2 that the number of holes outside of manufacturer's tolerance (below tolerance and over tolerance) does not trend significantly from year to year which implies that even the small number of outlying holes are not changing with time. There does tend to be more under-sized holes than over-sized holes and this is presumably linked back to the manufacturer's machining capability when drilling holes in the ACI stages.

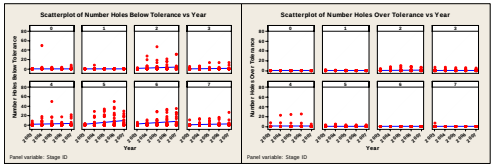

Figure 2. Scatterplot of number of holes below and over tolerance limit expressed as a percentage of the nominal diameter versus year for each ACI stage.

Typically the mean hole diameter for stages 2 to 7 did not vary from year to year by more than 0.001 mm (or 1 nm) and this is demonstrated in Figure 3 for Stage 2. In some instances the mean hole diameter for an ACI stage has remained unchanged for more than 5 years. Newer instruments have been plotted separately to give more clarity.

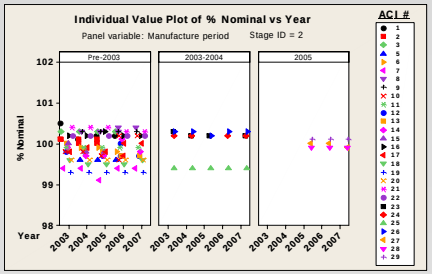

Figure 3. Plot of hole mean diameters of stage 2 for individual ACIs over a 5 year period, with newer instruments plotted separately.

This can also be seen for Stage 7 as shown in Figure 4

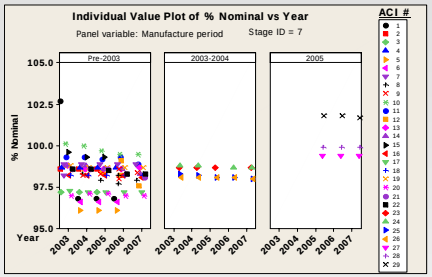

Figure 4. Plot of hole mean diameters of stage 7 for individual ACIs over a 5 year period, with newer instruments plotted separately.

This data demonstrates that the ACIs are not changing significantly with time and therefore the cleaning procedures within the 3M methods and the wear and tear of the instruments can be considered negligible. For all stages the year-to-year differences are significantly less than kit-to-kit differences. Within this time period there has been no occurrence of an ACI stage with a mean hole diameter outside the manufacturer's specifications.
ACI mensurations are typically performed in batches of 2 or 3 instruments throughout the year and therefore this is evidence of a very robust mensuration service and calibration procedure used by Copley Scientific Ltd for the Mitutoyo VIS, as recently reported (5).
It is important to note that this very good repeatability does not necessarily imply high accuracy. Also the control of mean nozzle diameter for each stage is far tighter than would be required for "in-use" CI specifications, ie the specifications required to provide accurate data for a pharmaceutical product.
The regular mensuration of USP ACI induction ports has also produced interesting information. The surface roughness of ACIs purchased prior to 2003 have a more variable roughness but this has been shown to be consistent from year to year. Newer kits tend to have lower surface roughness which is presumably related to improved manufacturing capabilities and again there is no evidence for an increase in roughness after use.

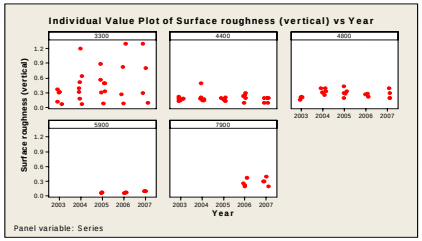

Figure 5. Plot of surface roughness for Induction Ports.

The mensuration of USP ACI induction ports has also shown consistent data for the internal diameter of the outlet from the induction port. The USP<601> states the bore should be 31.75mm with an upward tolerance of 0.50mm. It was found that early induction ports provided by Copley with an internal diameter of approximately 32.00mm resulted in a leak during the leak test and these induction ports were replaced. The induction ports in this publication are shown to be close to 31.90mm and this produces a good fit around the double O-ring of the ACI cone.

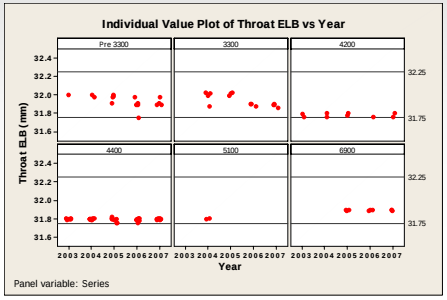

Figure 6. Plot of exit port internal diameter for the Induction Ports.

Conclusions

ACI stages and Induction Ports have been mensurated annually over a 5 year period and the data has been charted to demonstrate that all ACI instruments are fit for purpose during this time period. There have been no mensuration failures where the mean hole diameter for a stage is outside the USP manufacturer's specifications. The high repeatability of mean hole diameter does not necessarily prove accuracy of measurement and is far tighter than would be required for "in-use" CI specifications for inhalation products.
Procedures are in place to ensure that the instruments are cleaned and maintained at a high standard and it has been demonstrated that there is no significant change due to wear and tear.
Copley Scientific Ltd provide a highly repeatable mensuration service and their calibration approach for the Mitutoya VIS is very robust.

Acknowledgement

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References

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