Recognizing the 25th anniversary of the Next Generation Impactor (NGI™): Early manufacturing considerations

In this interview, Daryl Roberts and Jolyon Mitchell reflect on manufacturing considerations encountered during the early commercialization of the NGI.

Editor's note

June 2026 marked the 25th anniversary of the shipment of the first Next Generation Impactor—the NGI™. In the late 1990s, the NGI Consortium of pharmaceutical companies (see sidebar) defined the need for and the performance requirements for the NGI and awarded a contract to MSP Corporation (St. Paul, Minnesota, US) to devise a suitable impactor. With substantial input from Consortium members, the NGI was then designed, patented and manufactured by MSP Corporation. The NGI has since become the preferred multi-stage impactor across the inhalation community.

In April and August 2016, two members of the development team, Daryl Roberts, PhD, and Jolyon Mitchell, PhD, published a two-part series in *Inhalation* that discussed manufacturing considerations for the NGI. The first article focused on nozzles while the second described collection cups and jet-to-plate distance.

To recognize the NGI's 25th anniversary, *Inhalation* is happy to republish those articles in this issue, along with the following interview in which Daryl and Jolyon offer their insights and reflections on the early commercial manufacturing of the NGI. In addition, they have provided a brief reference list at the end of the interview.

Our congratulations to the entire NGI team—the NGI Consortium, its representatives and MSP Corporation—for their critical collaboration and an outstanding invention!

Vicki Schuman, Editor and Publisher, Inhalation: Daryl, what was your role in the manufacturing of the NGI?

Daryl Roberts: I was the Project Leader inside MSP Corporation during the development of the NGI under the sponsorship of the NGI Consortium. As the project evolved, I came to know every detail about the design of the NGI and each machine shop that made each part, as well as how to assemble the final instrument. I also wrote the inspection procedures and pass/fail criteria for each part of the NGI.

MSP was a small company in those days, probably fewer than 20 people with a highly skilled team of mechanical engineers and technicians who did the hands-on work. We also worked with machine shops in the Minneapolis/St. Paul, Minnesota area.

There are real artisans in the world of machining and mechanical engineering. The precision and accuracy they can routinely achieve, to the thousandths of an inch, with high yields, is amazing.

Inhalation: What were some of the biggest challenges in manufacturing the NGI?

Daryl: Achieving the precision requirements for each and every part, including the nozzles. The nozzle precision at each stage is ± 1% of the nominal nozzle diameter but not larger than 0.05 mm and not smaller than 0.01 mm. The contract machinists we worked with would do on-site, in-person inspections of the nozzles using our optical inspection instru-

ments to check for small burrs or other flaws on the parts they made for us. Those inspections helped substantially in perfecting the nozzles. We also learned a lot about electropolishing.

One day I received an e-mail with photos of an NGI (with a serial number greater than 500), that had been relayed from an irritated customer who was complaining about the nozzle on stage one being "out of round." While we found a mistake that was occurring at one of our machine shops, surprisingly our investigation revealed that testing a nozzle with a go/no-go pin gauge is insufficient to determine whether it has the correct diameter. We then launched into a study of nozzle roundness on all stages and implemented a quantitative specification of roundness for all future nozzles.

Another surprise was in receiving a returned NGI that had substantial corrosion all over the unit. We traced the problem to residual acid from the anodization of the aluminum bottom frame. The situation reminded us that when selling hundreds of a single system, it's not possible to be 100% perfect. Still, we strived for perfection as we continued to make and sell NGIs.

Inhalation: Jolyon, what was your role in the manufacturing of the NGI?

Jolyon Mitchell: I was a member of the Executive Committee of the consortium of pharmaceutical companies that established the performance specifications for the NGI, funded its development and guided the design through to the final product. I was also the consortium representative who supervised the two archival calibrations of the NGI.

In early 2001, as the industry began to purchase NGIs from MSP, it became evident there would be a need to ensure its quality and to communicate its desirable design attributes to pharma members who were not part of the NGI Consortium. In that context, I helped launch the European Pharmaceutical Aerosol Group (EPAG), along with the group's leader, Dr. Steve Nichols. We and others were a small team of knowledgeable professionals who purposely followed the successes and problems of the NGI as it started to proliferate into the inhaler testing community.

EPAG's work included the writing of several articles to demonstrate how the NGI performed with the different inhaler device types. At that time, I was Scientific Director at Trudell Medical International and involved in the evaluation of the NGI when testing pressurized metered dose inhalers in combination with valved holding chambers, and when testing a novel breath-actuated jet nebulizer. For each inhaler type, issues came to the foreground. Examples included how to interface a valved holding chamber or nebulizer with the NGI and breathing simulator and how low the flow rate through the NGI could be when evaluating those products as they mimicked young pediatric use.

Inhalation: What issues did you and your EPAG colleagues help MSP solve for the first 50 to 100 NGIs?

Jolyon: Many of the NGI parts, such as the lid, the seal body and the pre-separator were coated with nickel. The purpose of the nickel coating was to maintain electrically conductive surfaces to eliminate static-charge build-up. Users saw frequent tarnishing of those parts, especially the pre-separator. Therefore, we encouraged users to take pictures of the parts so that MSP could review and take corrective action. It turns out there are a host of detailed issues, including part cleanliness and the specific chemistry of the nickel-containing plating baths, that affect coating nickel onto aluminum, with its troublesome natural oxide surface layer. These issues were eventually ironed out with regular feedback to MSP from industrial users.

Inhalation: Did you encounter any difficulties transitioning to the NGI from the Andersen Cascade Impactor?

Jolyon: Not really. In fact, I noticed an immediate improvement in productivity in terms of the number of APSD characterizations that could be done each day, largely due to the NGI's simpler single-body design that avoided placing stages in the wrong order. The Andersen Cascade Impactor (ACI) requires complete disassembly after each run to recover the collected fractions of the active pharmaceutical ingredient on the stages.

In this respect, another important feature of the NGI was the introduction of the frame, which requires only a single action to assemble all the collection cups for insertion into the body of the NGI.

Inhalation: Were there problems with particle/droplet bounce on the collection cups?

Daryl: The collection surfaces of the cups in the first 25 or so NGIs were smooth at the micron size scale, just like native sheets of stainless steel. This surface caused aqueous solutions to "bead up" periodically and made it difficult to apply coatings to minimize particle bounce. Coating with a surfactant was not entirely satisfactory either because when the air flow started, this material tended to move away from the cup surface immediately underneath each of the nozzles of some stages. MSP solved this coating problem by purposely roughening the surface with glass beads, achieving a surface roughness in the range of 0.5 micron to 2.0 micron, as described in the second republished article in this issue. The problem was resolved satisfactorily and customers continued to successfully coat using a

thin layer of a nonionic surfactant (sold commercially as Brij 35) and other methods.

Inhalation: What would each of you do differently in constructing the NGI if you were to do it again?

Daryl: From the outset, I would make all the parts, except the bottom frame, out of 316 stainless steel (316SS). We spent too much time with nickel coating and precision issues related to it and with corrosion of 304 stainless steel. There's no material like 316SS; it has reasonable machining costs and high mechanical and chemical stability.

Jolyon: On reflection, I would have addressed the corrosion resistance issue earlier, through my contacts in EPAG. I had experience using ACIs machined from 100% 316SS in the 1980s, when those impactors were available commercially only in aluminum. So I was aware of the need to optimize corrosion resistance. In the end, after corrosion issues with the nickel-coated Micro Orifice Collector (MOC) had become apparent, it took up to serial number 640 for MSP to make the change successfully to 100% 316SS (as discussed in the first republished article).

Members of the NGI Consortium

As recognized during the development and early user experiences with the NGI, "considerable technical input was obtained from representatives from all the sponsoring companies and their technical staffs; their input is gratefully acknowledged." [1] The Consortium representatives and their affiliated companies were:

Lars Asking (AstraZeneca R&D Lund)
Jeremy Clarke (Vectura, Ltd.)
Tön Forch (Pharmachemie)
Beatrix Fyrnys (Asta Medica—later Sofotec GmbH)
David Ganderton (Coordinated Drug Development, Ltd.)
Bernie Greenspan (Dura Pharmaceuticals)
Dieter Hochrainer (Boehringer Ingelheim Pharma KG)
Mike Holroyd (Norton Healthcare—later IVAX Pharmaceuticals)
Hans Keegstra (Pharmachemie)
Jari Kovalainen (Orion Pharma)
Terhi Mattila (Orion Pharma)
Paul Miller (Pfizer)
Jolyon Mitchell (Trudell Medical International)
Steve Nichols (Aventis Pharma)
Bo Olsson (AstraZeneca R&D Lund)
Dilraj Singh (Novartis Pharma AG)
Keith Truman (GlaxoSmithKline)
Mike Van Oort (GlaxoSmithKline)
Dave Warren (3M Healthcare, Ltd.)
Bruce Wyka (Schering-Plough Research Institute)

Inhalation: Thank you both for your thoughtful reflections on the early days of manufacturing the NGI.

Again, our congratulations to the entire NGI team—the NGI Consortium, MSP Corporation and the many dedicated machinists and assemblers who continue to play their critical role—on the 25th anniversary of shipping NGI serial number one.

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Daryl L. Roberts, PhD, President, 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, President, Jolyon Mitchell Inhaler Consulting Services, Inc., London, Ontario, Canada. Tel.: +1 519 472-5364, mitchelljolyon@gmail.com

The Next Generation Impactor (NGI™)—Manufacturing Control: Part I. Nozzles

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

Daryl L. Roberts, PhD
MSP Corporation

Jolyon P. Mitchell, PhD, FRSC(UK), CChem, CSci
Jolyon Mitchell Inhaler Consulting Services, Inc.

The multi-stage cascade impactor (CI) has 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, such as fine particle fraction. There are several designs of CI in the pharmaceutical compendia from which the developer of an OIP may choose for inhaler evaluation. However, it is only since the development of the Next Generation Impactor (NGI™) at the turn of the 21st century that there has been an apparatus purpose-built for testing of OIPs.[1]

This article is the first of two explaining the rationale and outcomes of the manufacturing controls for the NGI (now over serial number 1,300) that have been devised in the past years. The first article emphasizes improvements in the control of the stage nozzle diameters, because that feature is the most important one affecting the aerodynamic size-fractionating performance of the impactor. The second article will explain the importance of both fixing and controlling the distance from the nozzles to the collection surface ("jet-to-plate" distance), as that parameter is the second-most important factor affecting the aerodynamic size-fractionating performance of the impactor.

In the late 1990s, the pharmacopeial compendia recognized a variety of CI apparatuses, including the Andersen eight-stage, non-viable impactor (ACI), the four-stage and later five-stage, multi-stage liquid impinger (MSLI), and the five-stage Marple-Miller impactor (MMI™). Apart from the last example, which utilized sample collection cups enabling easier API recovery than from flat plates, the other apparatuses had been developed for non-pharmaceutical use. In the case of the ACI, its original purpose was as a room air quality sampler, hence, the then-standard operating flow rate of one actual cubic foot per minute (ACFM; equates to 28.3 L/min) was used initially for the evaluation of pressurized metered-dose inhalers (pMDIs). Importantly, none of these apparatuses had a robust manufacturing specification resistant to effects that might reduce precision and accuracy for the control of the diameter of the nozzles associated with each stage; yet these diameters are the primary critical measures that determine the aerodynamic size at which a given stage size-fractionates the incoming aerosol particles.

Furthermore, the use of inappropriate materials for manufacture (albeit acceptable for environmental aerosol sampling) resulted in performance changes with repeated use in the more chemically challenging role as an apparatus for laboratory testing of pharmaceutical products. In particular, unanodized aluminum was the standard material in the manufacture of ACIs, a material that is relatively soft compared with stainless steel. However, more importantly, aluminum is amphoteric, resulting in reports of significant corrosion from contact with either acidic or alkaline solutions.[2] In addition, aluminum immediately forms a non-conducting oxide layer when exposed to air, resulting in the potential for surface electrostatic charge accumulation that may then interfere in testing certain OIP classes, particularly dry-powder inhalers (DPIs) but also including pMDIs, whose aerosols are intrinsically charged during the atomization process.[3] Because of instability in materials of manufacture, users were forced to recalibrate their CIs with monodisperse particles of known aerodynamic diameter covering the overall size range within which the apparatus functioned, a process that could take

upwards of a month per CI to complete at considerable expense. Adaptations were subsequently developed to the basic ACI configuration to permit its use at selected flow rates in excess of 28.3 L/min for the assessment of aerosols from DPIs.[4] But again, there was no robust manufacturing specification for these modified stages and these designs violated the then-known nearness-of-nozzles criterion,[5] with the potential for reduced accuracy and precision in the size fractionation process for the affected stages.

In addition, the design of the pre-separator used with the ACI primarily for DPI assessments resulted in poor size-selectivity compared with that of the impaction stages. Consequently, the effective cut-off diameter (ECD), defined as the size at which 50% of the incoming particles are collected, was so close to the ECD of the first ACI stage that it starved that impaction stage of particles that should otherwise have penetrated to this component.[6] The MSLI and MMI could have been chosen as alternatives to the ACI, but the industry-required resolution of at least five data points for the measured APSD within the critical range of 0.5 to 5.0 μm aerodynamic diameter, particularly for US-based regulatory submissions, effectively precluded their use.

To avoid these and other technical deficiencies and enable a truly user-friendly experience for inhaler testing technicians, the pharmaceutical companies who sponsored the development of the NGI established a robust set of "must" requirements for this new impactor (Table 1).[1]

The development program included the manufacture and testing of an "archival" NGI whose individual stage nozzle diameters were manufactured to be as close as possible to their nominal design values, a step that avoided the need for periodic and lengthy calibrations of individual NGIs with reference particles with known aerodynamic diameter. The archival apparatus was calibrated using reference particles at 15, 30, 60 and 100 L/min,[7,8] thereby establishing an archival calibration defining the aerodynamic performance for all NGIs, provided their stage nozzle and other critical dimensions remain within the tolerance specified in the pharmacopieal compendia.

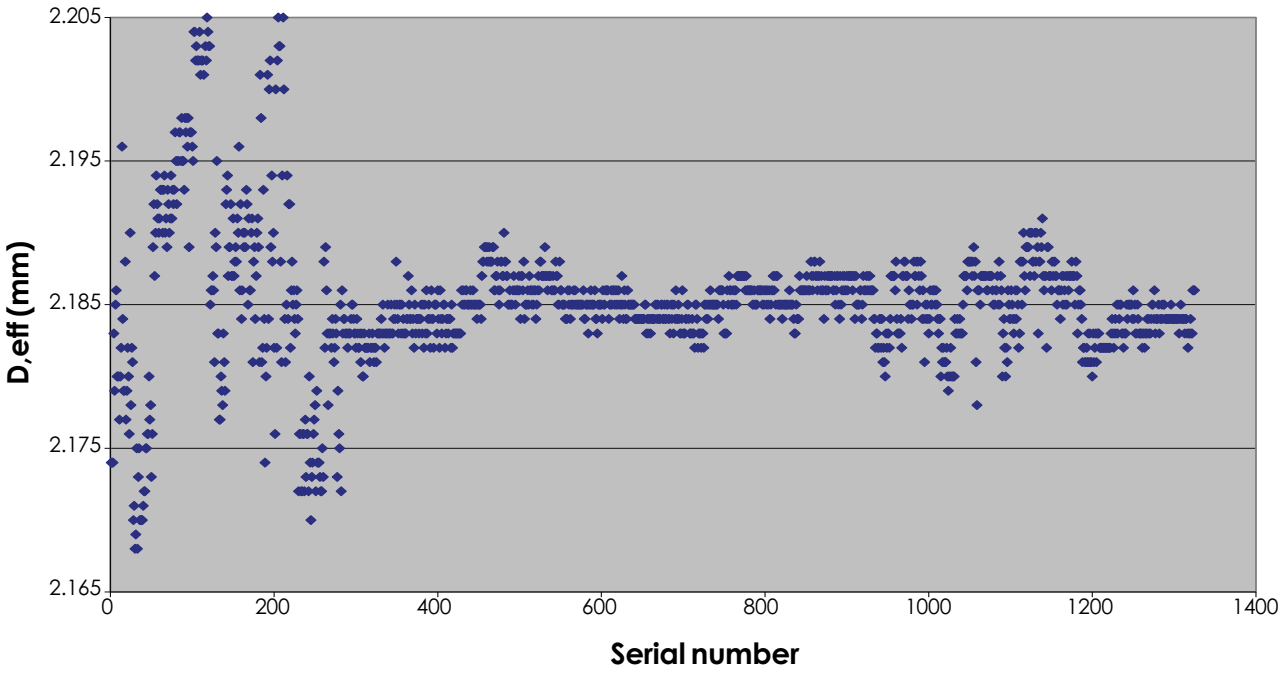
The NGI met these "must" requirements from the outset. However, the manufacturing, which now takes place under an ISO 9001 quality system, has improved in the past 15 years to address the issues of long-term, routine use in a regulatory environment. These improvements have been implemented hand-in-hand with a heretofore absent theoretical understanding of the performance of multi-nozzle cascade impactor stages, thereby providing traceability of APSD measurements to the international length standard.[9,10] Because of these traceable methods, users can be confident that when MSP Corporation shipped NGI™ serial number 1,300 in early 2016, it performed aerodynamically in the same manner as the first NGI that MSP shipped in June 2001. And now, even more importantly, users can expect to retain APSD measurement precision in routine use for the foreseeable future, **provided their NGI is well-maintained**.

Table 1

"Must" Specifications for the Next Generation Impactor

M-1	Automatable (but suitable for manual operation); Manual system must be equivalent to automated system; Flow paths must be identical for manual and automated equipment
M-2	Operates over a range of flow rates from 30-100 liters per minute
M-3	Calibration data for the flow rate range of 30-100 liters per minute are available; *Published specification that fully defines performance and engineering tolerances
M-4	Capable of fully characterizing the "less than 10 µm" cloud size range
M-5	Needs right number of stages at right cut-offs (independent of flow rate) *Minimum of 5 stages 0.5-5 µm; One stage between 5 and 10 µm plus high capacity stage at 10 µm or higher (pre-separator)
M-6	The stages will be followed by a micro-orifice filter that is 90% efficient for particles larger than or equal to 0.2 µm aerodynamic diameter (or smaller particles)
M-7	Efficiency curves for stages must be appropriate *Efficiency curves as steep as possible (GSD for stages <1.2) *GSD for all stages similar *Overlap between stages is minimized
M-8	Deposition profile unaffected by stage loadings (up to 10 mg)
M-9	Operates using defined entry conditions * Basic design of USP throat is acceptable for initial design => needs improved connectivity => must be "designed for manufacture" Accepted that current throat is *in vitro* model
M-10	The empty volume of the impactor must be no more than 1.5 liters, measured from the inlet of the USP inlet to the exit of the impactor body, including the preseparator
M-11	Low wall losses; Not more that 5% on any stage and not more than 5% total on all stages
M-12	Good drug recovery (mass balance) * Less than 2% carryover between successive determinations for same strength products * Drug must be at a level of "not detectable" when changing between products
M-13	No bounce/re-entrainment *Collection substrate prevents re-entrainment
M-14	Capable of being grounded; Unaffected by static
M-15	Physically robust
M-16	Constructed using inert/robust materials (can use common solvents); No extractives from o-rings
M-17	Good accuracy and precision (± 5%)
M-18	Operator independent (No statistical difference between results between independent laboratories)
M-19	Acceptable to regulators/Pharmacopoeia
M-20	Designed and manufactured to ISO 9000 or equivalent
M-21	Applicable to all single shot inhaled delivery systems (MDIs, DPIs, aqueous inhalers)
M-22	Easy to qualify and validate in the laboratory Acceptance criteria based on quality control of jet sizes
M-23	Fast *Cycle time of less than 30 minutes for manual determinations *Automated cycle time to be reviewed later

Figure 1



Nozzle diameter: The core of cascade impaction

As the first approximately 100 NGIs were produced, early reports by users were positive.[11] In some cases, regulators requested a comparison of the historical ACI to the newly available NGI.[12] Despite this favorable reception, to the surprise of one of us (DLR), the user community did not have a definition of an acceptable nozzle diameter, much less for the large number of nozzles on a typical impactor stage.

Furthermore, a quantitative definition of an acceptable nozzle diameter or "average" diameter for a multi-nozzle stage was absent from the international pharmacopeial compendia (USP, Pharm Eur and equivalent), even though at the same time, the idea was articulated in the USP that periodic verification of the nozzle diameters by optical inspection, termed "stage mensuration," would be worthwhile. They stated, "Because jets can corrode and wear over time, the critical dimensions of each stage, which define that impaction stage's calibration, must be measured on a regular basis. This process, known as stage mensuration, replaces the need for repetitive calibration (using standard aerosols) and ensures that only devices that conform to specifications are used for testing inhaler output."[13]

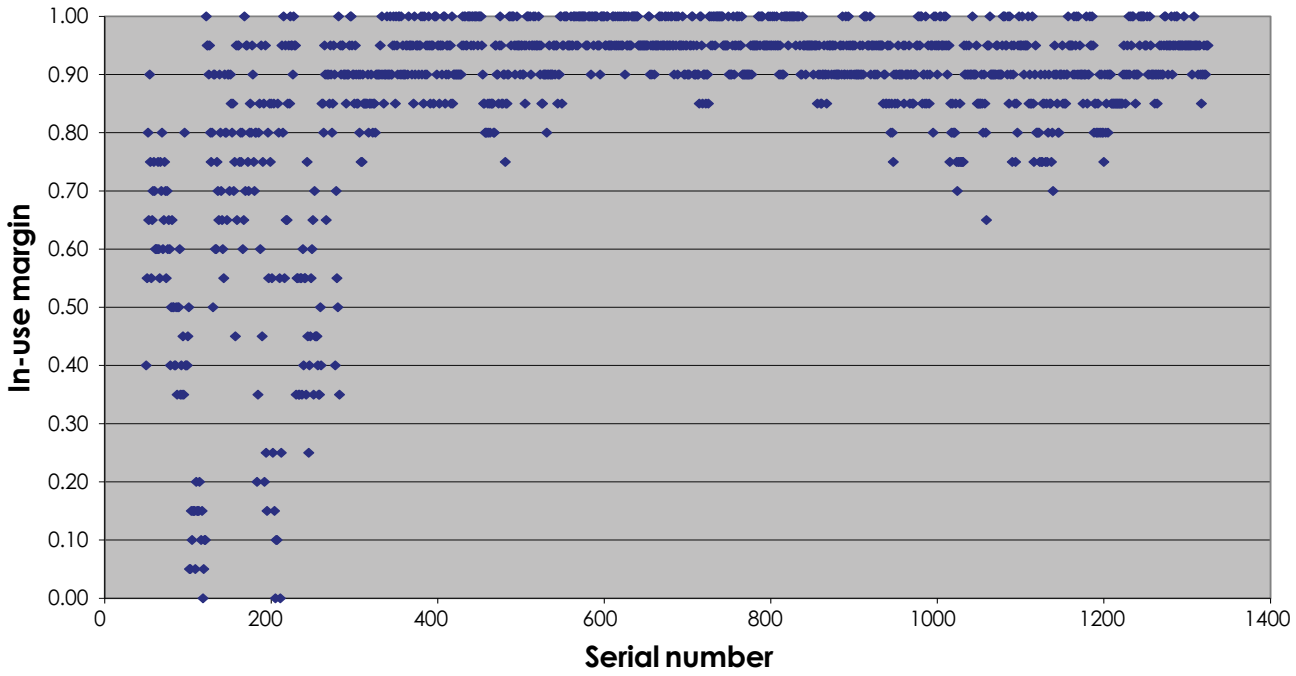
A quantitative definition of nozzle tolerance had already been articulated in the NGI design paper.[1] Indeed, this definition came to the European Pharmacopoiea in September 2004[14] and to the United States Pharmacopeia in January 2005,[13] several months before the nozzle dimensions of the 30-year-old Andersen impactor came to the USP in April 2005.[15] However, as users began to have "used NGIs" and sent them to MSP Corporation for stage mensuration, they consistently wanted to know what to do if one or more nozzles were found to be outside the requirements for a new impactor, as defined in the USP/Ph.Eur. The answer to this question was provided by extending the theory of inertial impaction to include a definition of Effective Diameter (D,eff) as a measurable "average" nozzle diameter defining the aerodynamic performance of a multi-nozzle stage.[9,10] This process, by eventually linking stage cut-off diameter to D,eff through measurable quantities, established the basis for a proper interpretation of stage mensuration data in terms of CI performance for measuring OIP APSDs. But perhaps more importantly, it made us think more about what the specifications should be for a **truly acceptable** impactor **at the time of its manufacture**.

Effective diameter, new impactors and in-use margin

No user wants to buy a product that, after one use or a few uses, goes out of specification. So although the USP and our own design paper placed a tolerance range on nozzles for newly manufactured NGIs, we at MSP had to ask ourselves whether anyone would really consider an impactor "in specification" if all of the nozzles were on the edge of the compendial tolerance range. Or worse, would nozzles of a given CI truly be "in specification" if alternate stages had nozzles on the opposite extreme edges of their tolerance range? Because most users have multiple CIs, we consider that either of these "technically in specification" outcomes are, in practice, burdensome situations for users. In the first of these cases, out-of-tolerance (OOT) results at the time of optical inspection a year later are virtually assured. In the second example, even the best technician is not going to achieve mass-per-stage equality from one

Figure 2

In-use margin of all stage 3 NGI nozzle pieces (24 individual nozzles per nozzle piece)



impactor to another, even assuming that the OIP-delivered aerosols have the exact same APSD, also inevitably leading to an OOT situation.

The reason that the introduction of the concept of "effective diameter" (D,eff) was so important is that it established, in terms of impactor theory, an analytically meaningful "average" diameter for judging the aerodynamic performance of a given impactor stage (Equation 1.):

$$D,eff = (\text{Area mean diameter})^{(2/3)} \bullet (\text{Area median diameter})^{(1/3)} \quad [1]$$

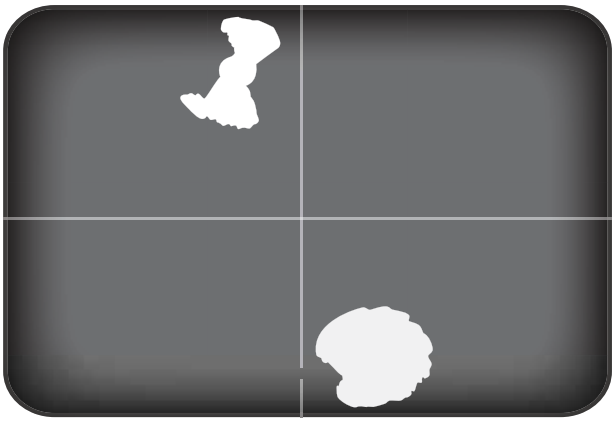
This relationship, applied to each size-fractionating stage, is sufficient to assess acceptability of the aerodynamic performance of the entire CI. To make it even easier for users to see at a glance whether their NGI is likely to remain in specification **during use,** we have now defined the In-Use Margin (IUM) as a measure of how close the given CI stage is to its tolerance limit (Equation 2):

$$IUM = \left(\frac{\text{Tolerance} - |\text{Nominal Diameter} - \text{Effective Diameter}|}{\text{Tolerance}}\right) \bullet 100\% \quad [2]$$

IUM quantifies where the aerodynamic performance is in relation to the tolerance range for a given CI stage. Thus, an IUM value between 0% and 100% indicates that the stage is acceptable aerodynamically. An IUM value of 100% means that the (D,eff) of the stage is **exactly** equal to the nominal design value; an IUM value of 0% means that the D,eff of the stage is **exactly** on the edge of the tolerance for the stage. And finally, if the IUM value is less than 0%, the stage fails the used impactor acceptance criteria.

Figure 3

Example of nickel detachment from the nozzles of the MOC



MSP has tracked the IUM of every multi-nozzle stage (more accurately called a "nozzle piece" because a stage includes the collection surface as well as the nozzles) for every new NGI. For the first 400 or so NGIs, the IUM values were merely "whatever they happened to be." But to respond to the reasoned user desire to ensure that their particular NGI does not go out of specification quickly, we improved our own internal acceptance criteria to be that all **new** nozzle pieces have an IUM of at least 50%. Achieving this goal enabled users to be far more confident that an annual optical stage mensuration would enable sufficient quality control for any individual impactor, substantially reducing the probability of OOT results.

Figure 4

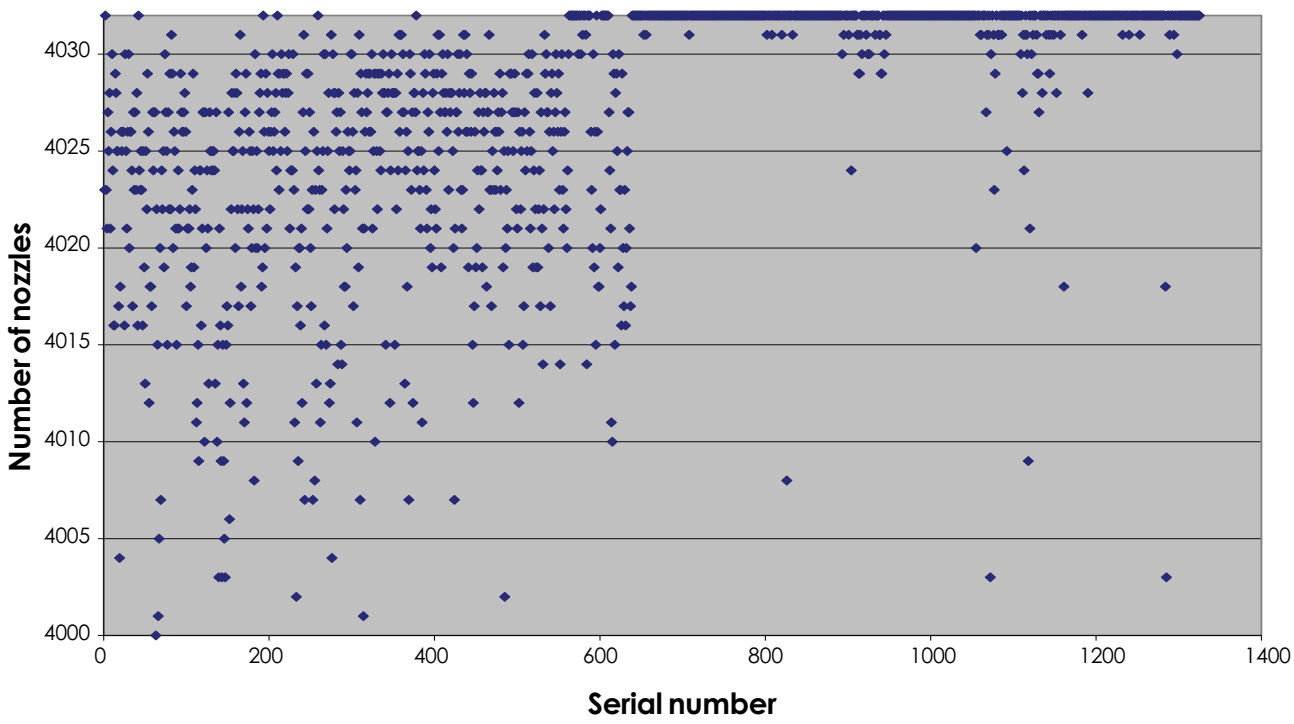
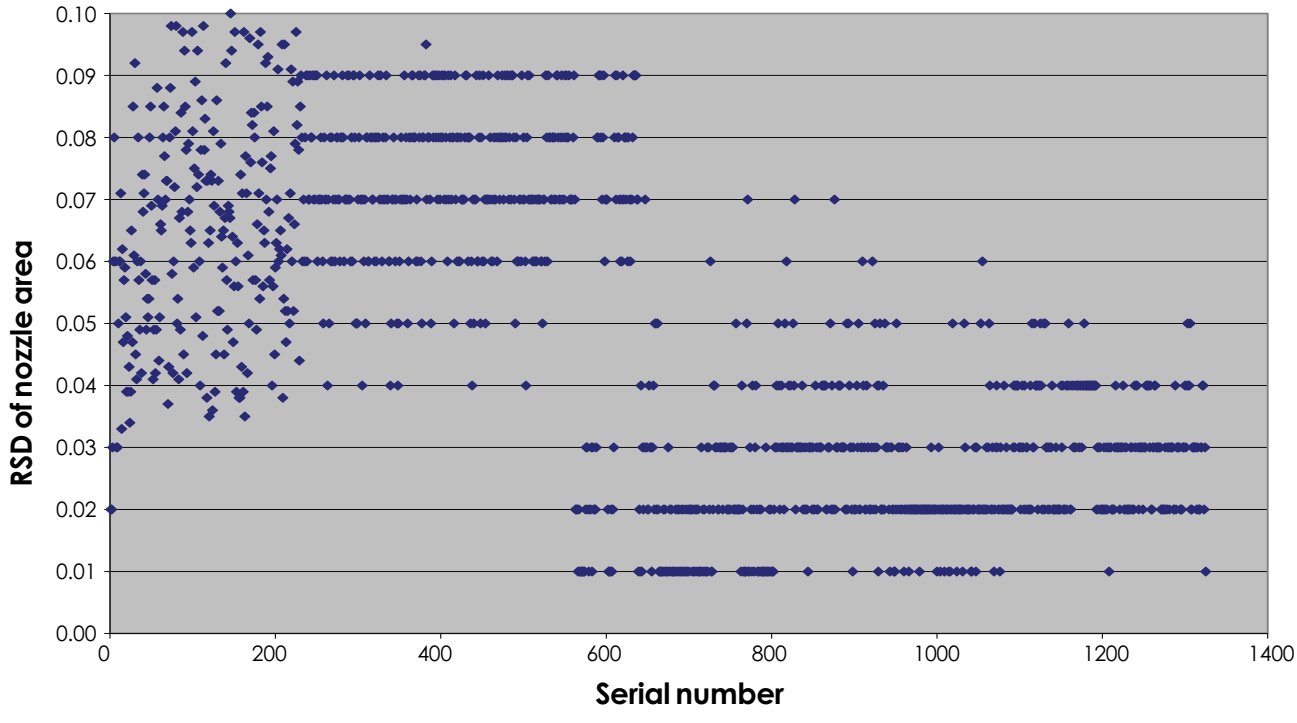


Figure 5



As an example, Figures 1 and 2 show values of (D,eff) and IUM for all stage 3 nozzle pieces for NGIs having serial numbers from 1 to over 1,300. The specification for all new nozzles on stage 3 of the NGI is 2.185 mm ± 0.020 mm, so that the range of the y-axis in Figure 1 has been scaled from 2.165 mm to 2.205 mm (a tolerance of ± 0.020 mm). Early on, until we truly understood and could therefore control nozzle manufacturing methods at the micron-size scale, we were happy to get nozzle sets "in specification." As a result, for NGI serial numbers between 1 and approximately 400, there were some nozzle pieces with zero IUM and some with 100% IUM.

After mastering the elimination of small burrs and other potential physical defects, as well as observing nozzle piece after nozzle piece by microscopy-image analysis, we have been able to coach our machinists to hit the mid-point the first time, all the time, by intention rather than just hoping that the nozzles would be in the "mid-range" of tolerance.

This type of quality monitoring at manufacture gives us the ability to respond proactively if any manufacturing process starts to drift away from its norm. For example, in Figure 1, it appears that the accuracy of the stage 3 nozzles began to drift between serial numbers 900 to 1,200. Once a trend or an amplification of random variation from the norm is detected, root-cause analysis can take considerable time and effort. However, by being proactive, we found that we can control the IUM to be well within the middle of its acceptable range even when we are solving problems that may have come up. (Our worst IUM figure in this time period was 65%.)

Nozzle control and the micro-orifice collector

The micro-orifice collector (MOC), comprising 4032 nozzles, each close to 70 microns in diameter, is an innovative concept that replaces the traditional back-up filter following the size fractionating stages of a CI. (A filter can be difficult to service in a semi- or fully-automated NGI system.) From the outset, we did not associate an "effective diameter" nor an "in-use margin" with this nozzle piece because its function is qualitatively different than that of a traditional impaction stage. Nevertheless, the robust nature of this component is critical to the long-term viability of an NGI of any given serial number.

Early users told us that the nickel coating on the MOC could be removed from time to time with cleaning, especially if aggressive (Figure 3). We addressed this concern by learning to manufacture each MOC in 316 stainless steel without any nickel coating. Furthermore, we can now routinely achieve highly round nozzles with all 4,032 nozzles fully open (Figure 4); the USP specification merely calls for more than 4,000 nozzles to be open. The nozzle sizes on the MOC now are substantially more uniform, resulting in a much smaller relative standard deviation associated with the diameters of the nozzles on the MOC (Figure 5). Furthermore, users are more free to implement appropriately aggressive cleaning strategies in routine use, so as to avoid OOT results.

Conclusions

The NGI is the first CI developed intentionally for the purpose of laboratory assessment of aerosols from OIPs, and the design was guided by a corresponding set of user-defined requirements. Consistent and improved manufacturing has been key to meeting the demands for high quality from industrial users in their highly regulated environment. We devised the concept of effective diameter and its associated in-use margin to establish a quantitative measure of the quality of both new and used impactors. The challenges that we have had to address include micron-level control of nozzle diameters and premature failures of a now-outdated MOC manufacturing method. We have achieved manufacture of all NGIs such that the 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 improvements we have described in this article have provided users with assurance that their NGIs will continue to serve their intended purposes for many years to come.

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Daryl L. Roberts, PhD is Senior Vice President, MSP Corporation, 5910 Rice Creek Parkway, Shoreview, MN, 55126, US, Tel. +1 651 287-8110, droberts@mspcorp.com. Website: www.mspcorp.com. Jolyon P. Mitchell, PhD, FRSC(UK), CChem, CSci is an Affiliate Professor, Department of Pharmaceutical Sciences, Daniel K. Inouye College of Pharmacy, University of Hawai'i, at Hilo, Hawai'i and owner of Jolyon Mitchell Inhaler Consulting Services, Inc.

Watch for the second article in this series, on the importance of fixing and controlling jet-to-plate distance, which is the second-most important factor affecting impactor aerodynamic size-fractionating performance.

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

Daryl L. Roberts, PhD
MSP Corporation

Jolyon P. Mitchell, PhD, FRSC(UK), CChem, CSci
Jolyon Mitchell Inhaler Consulting Services, Inc.

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.

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

Figure 1

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

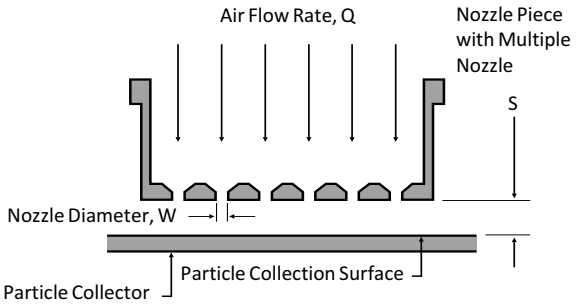
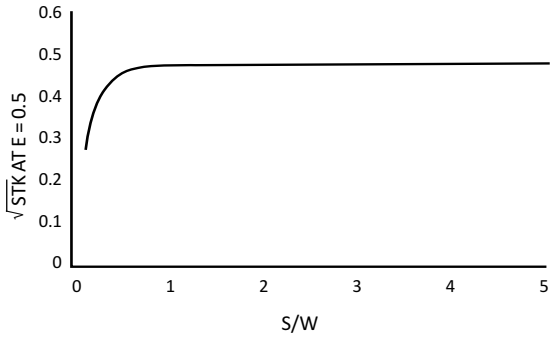


Figure 2

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])



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:

$$\sigma_{s/w}^2 = \frac{\sigma_s^2}{W^2} + \frac{S^2\sigma_w^2}{W^4} = \frac{1}{W^2}\left(\sigma_s^2 + \frac{S^2\sigma_w^2}{W^2}\right) \quad [1]$$

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).

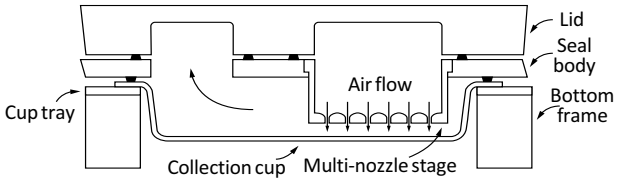
The controlled dimensions of each part influencing the S/W value for each NGI is indicated in each certificate of conformance for each NGI. Furthermore, in the NGI, since the nozzle pieces are fixed in place by a metal-to-metal interference fit, not adjustable or removable by the practicing technician, 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

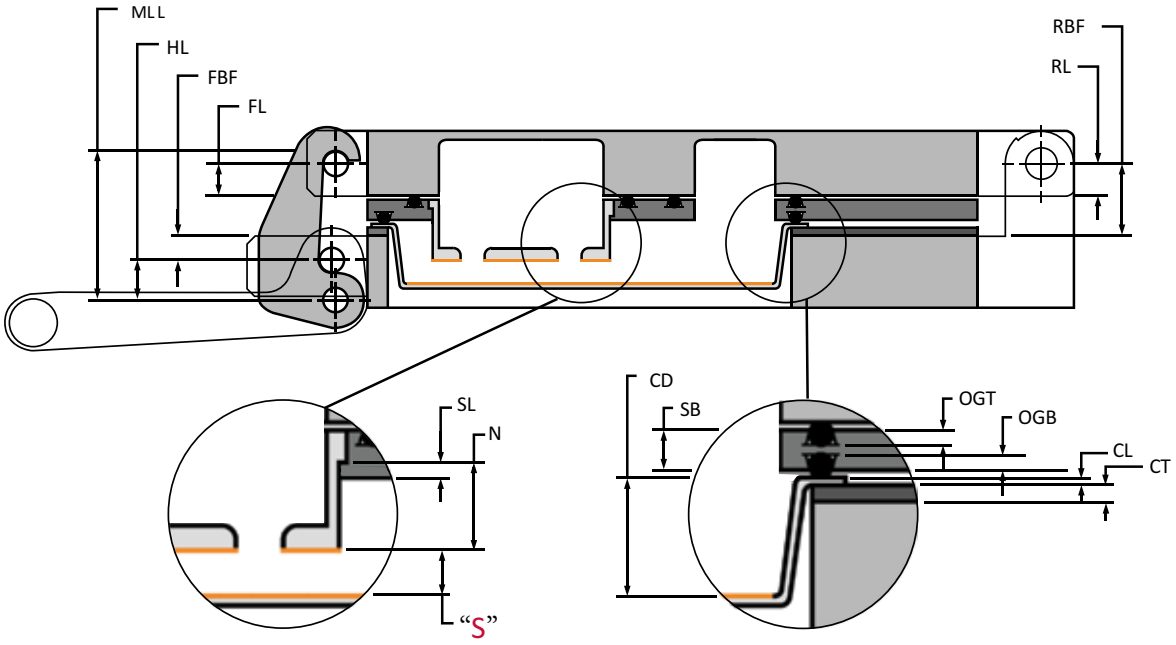
Table 1

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

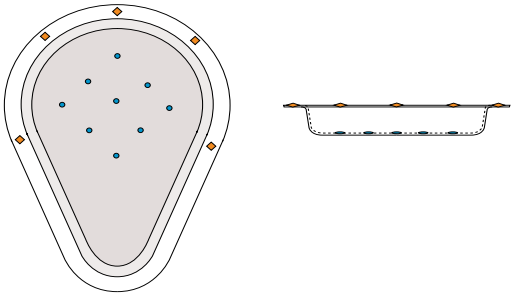
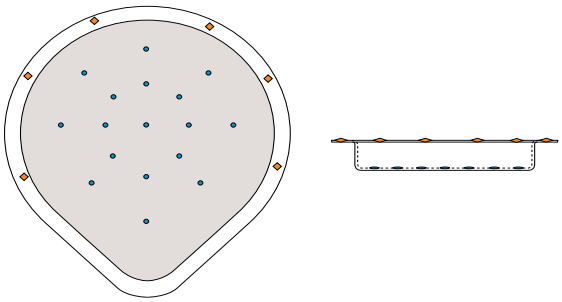


Figure 6

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

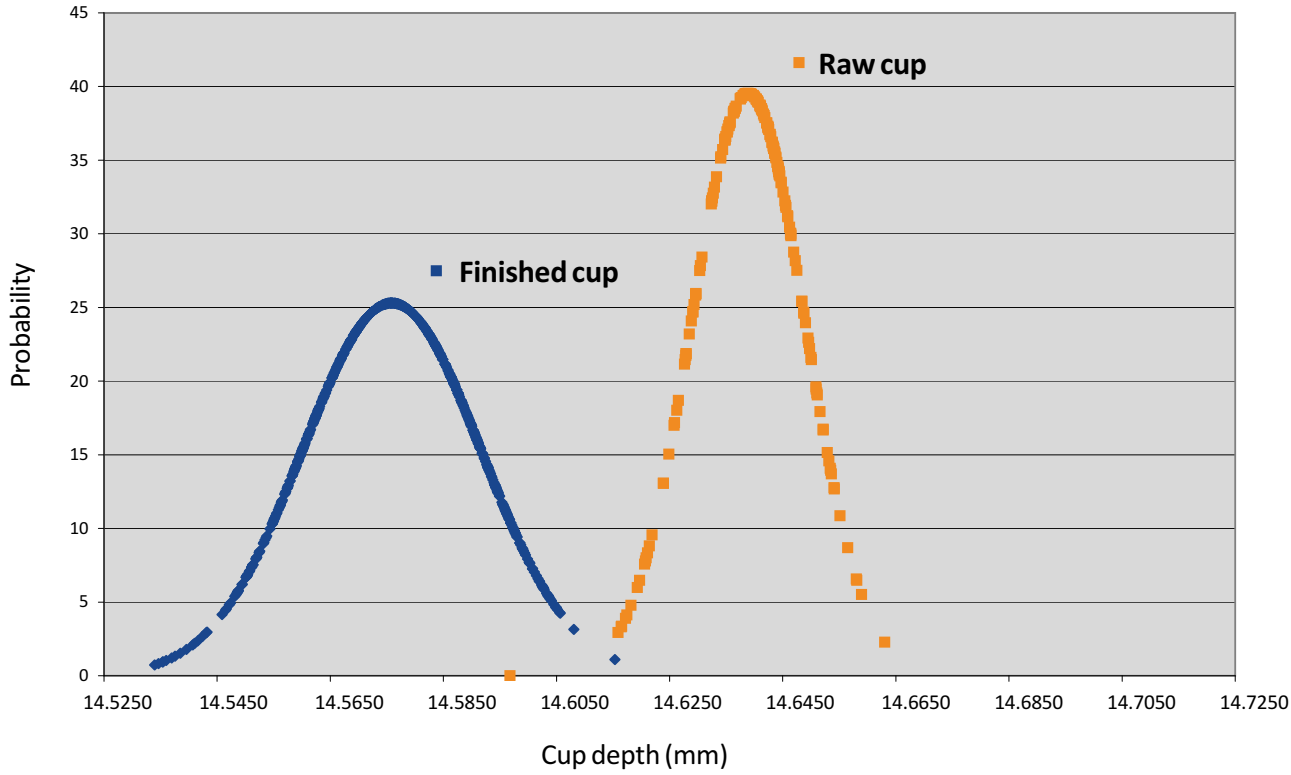
Machined cups in the first approximately 25 NGIs

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.

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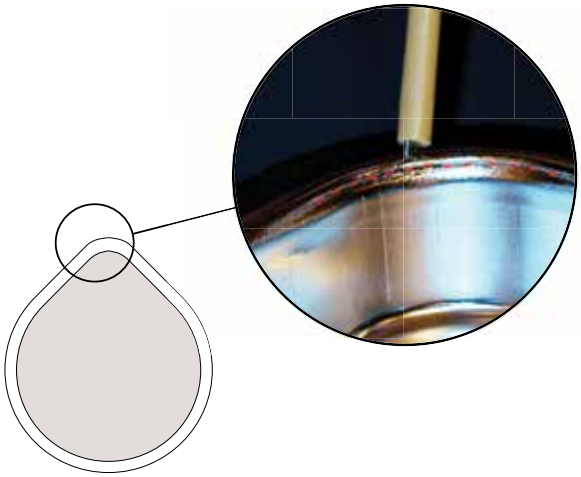
Figure 10

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



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Daryl L. Roberts, PhD is Senior Vice President, MSP Corporation, 5910 Rice Creek Parkway, Shoreview, MN, 55126, US, Tel. +1 651 287-8110, droberts@mspcorp.com. Website: www.mspcorp.com. Jolyon P. Mitchell, PhD, FRSC(UK), CChem, CSci is an Affiliate Professor, Department of Pharmaceutical Sciences, Daniel K. Inouye College of Pharmacy, University of Hawai'i, at Hilo, Hawai'i and owner of Jolyon Mitchell Inhaler Consulting Services, Inc.

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