Optimizing the role of automation in variability reduction strategies for delivered dose uniformity (DDU) and aerodynamic particle size distribution (APSD) testing of inhaled drug products

Semi-automation can enhance the quality of inhaler test data, while at the same time boosting productivity; choosing which tasks to automate and appropriate technology is essential.

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The centrality of cascade impaction for the determination of emitted aerosol aerodynamic particle size distribution (APSD) in the development and manufacture of all orally inhaled products (OIPs) has stimulated multiple attempts at complete, end-to-end automation. Today, however, in most laboratories, it remains a predominantly manual, complex analysis prone to variability.[1] The same can be said of delivered dose uniformity (DDU) testing, which, though substantially simpler, shares many of the same automation challenges. In both cases, full automation has now been largely discounted as too costly and too high risk, with semi-automation—the use of smart, automated solutions for specific tasks—being the preferred strategy. Such solutions reduce variability and enhance data integrity, simultaneously releasing analyst time and boosting lab throughput. They can therefore offer an attractive economic return.

This article considers the issue of automation within the context of reducing the variability associated with inhaler testing, for both DDU and cascade impaction. A key focus is proven, easy-to-validate, modular solutions that can be used to tackle specific tasks. Experimental data illustrate the impact on variability that established solutions can have.

A strategy for automation

The reliance of the inhalation community on APSD and DDU data throughout the product lifecycle makes the idea of completely automating the associated techniques highly attractive. Automation has the potential to increase lab productivity and improve safety by reducing the risk of repetitive strain injuries (RSI) and exposure to toxic chemicals. Crucially, it can eliminate operator-to-operator variability and/or error, thereby improving data integrity, arguably the greatest prize. By reducing the number of out-of-specification (OOS) results and enhancing sensitivity, automation directly supports more effective decision-making from R&D through quality control (QC). However, fully automated solutions for inhaler testing involve major capital investment and significant running costs. The maintenance, training and other operational expenditures associated with these complex systems make the lifetime cost of ownership extremely high.

In practice, the realization and operation of fully automated systems has proven so costly and labor-intensive that the preference in most labs is, instead, for semi-automation—the progressive automation of individual elements of an analysis with easy-to-validate modular solutions. Semi-automation avoids the level of capital investment associated with complete automation, which is problematic in terms of both scale and timing. Unlike tablets, for example, most OIPs (dry powder inhalers (DPIs), especially) have a unique device/actuator design to deliver and aerosolize the formulation, requiring bespoke test methods that make a one-size-fits-all approach almost impossible. Investing early, at the development stage, maximizes returns but is high risk. The alternative strategy of waiting until post-approval reduces the opportunity for payback and introduces the issues of

method transfer and cross-validation from the manual techniques applied in R&D.

Partial or semi-automation can involve either customized or off-the-shelf solutions. The customized approach makes it possible to tackle product-specific issues with fewer restrictions but is associated with higher cost and risk. Off-the-shelf solutions are easier, with proven, low-cost technology available for common tasks. Semi-automation can proceed step-by-step, beginning in R&D, with success supporting further, more complex projects;[2] and, beyond flexibility, it offers a range of additional benefits.

For example, from an operational perspective, semi-automation solutions are more reliable, and substantially less demanding in terms of cleaning, maintenance and training, than fully automated systems. Furthermore, such solutions often automate only a single element of the analytical process, making it straightforward to return to manual testing if required. In addition, a semi-automated approach makes scale-up and method transfer relatively straightforward via the installation of additional parallel systems, or the use of solutions designed for the transition from R&D to QC, to directly transfer a specified method to a higher throughput design.[3]

In summary, a modular, semi-automation approach can deliver an appreciable measure of the benefits derived from full automation but at lower cost and with lower risk. Deciding which tasks to automate is the key to maximizing the value of an investment.

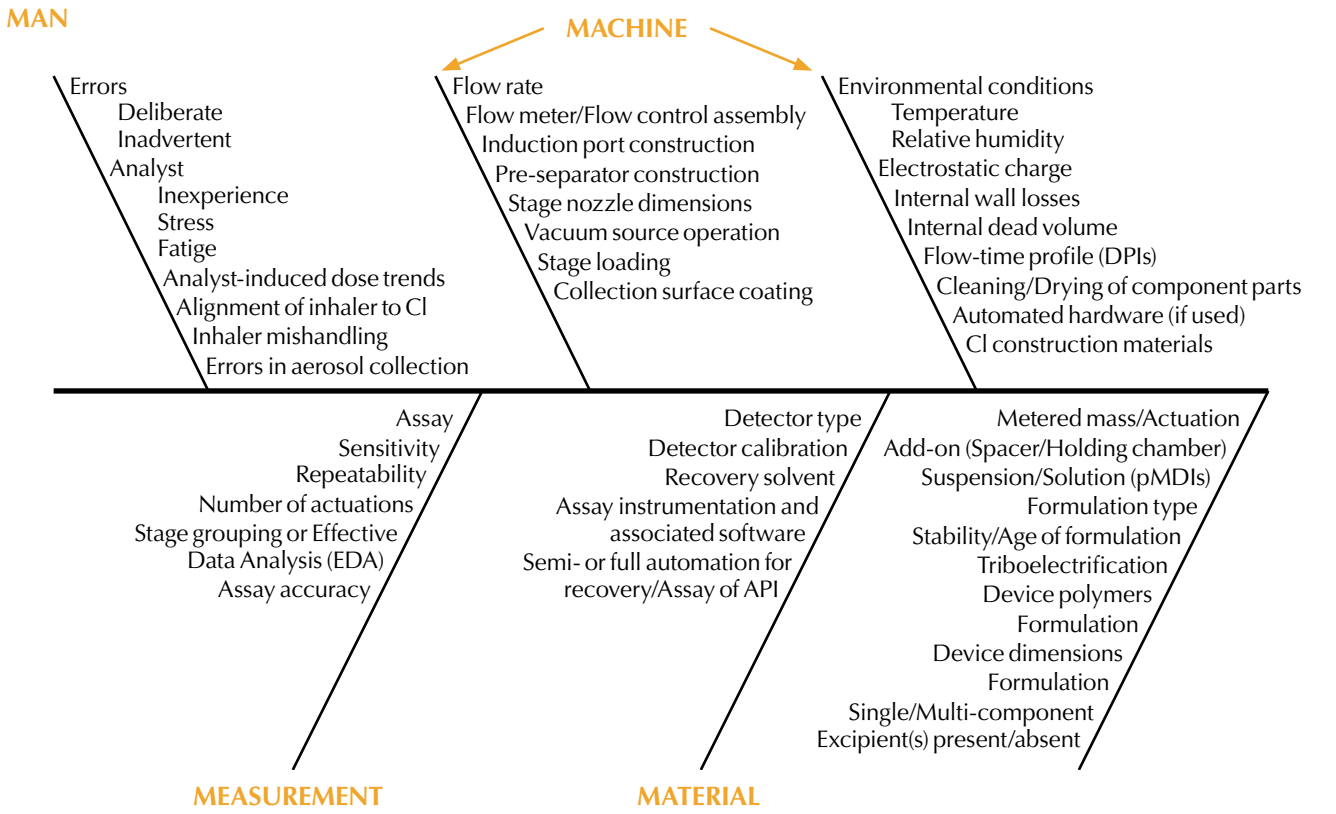
The process of variability reduction

Reducing the uncertainty associated with inhaler test data requires systematic consideration of all the factors that could give rise to variability and the development of an effective strategy to mitigate them. Automation is an important part of such strategies but other tools and practices play an equally critical role. Variability reduction in cascade impaction has notably been the focus of rigorous investigation over many years and the factors that give rise to it are now well-documented (Figure 1). There is also considerable advice in the literature regarding mitigation strategies.[1,4] Closer examination of these factors helps to illustrate the place of automation in the variability reduction toolkit.

For example, in Figure 1, temperature and humidity are both listed as variables that can impact the performance of the test equipment ("Machine"). Humidity is particularly problematic in the case of hygroscopic DPI formulations since the adsorption of even relatively low levels of water can directly affect particle release, dispersion and de-agglomeration. Temperature, on the other hand, or more specifically the thermal mass of the impactor, affects nebulizers, certain metered dose inhalers (MDIs) and soft mist inhalers (SMIs), as well as other aqueous droplet inhalers (ADIs); with evaporation leading to the under-sizing of droplets and an erroneous APSD for solution-based products. These issues may be addressed by environmental control systems for the laboratory or, more cost effectively, by dedicated accessories designed to con-

Figure 1

Many factors impact the uncertainty of cascade impaction results and a wide range of different mitigation strategies are required to tackle them. (Reproduced with permission.)[4]



trol the local test environment and/or the temperature of the impactor.[5]

The accumulation of electrostatic charge can also be detrimental to the accuracy of APSD measurements, particularly in low-humidity environments. Electrostatics can influence particle behavior within the impactor, causing deposition on the wrong stage or between stages, thereby compromising the mass balance that is a key system suitability metric. Precautions that can help to reduce this issue include the use of anti-static grounding kits, which typically include wrist bands, and bench- and floor-mounted mats, anti-static clothing and de-ionizers. Using metal, rather than plastic, induction ports/throat models (where adopted)[6] can also be beneficial.

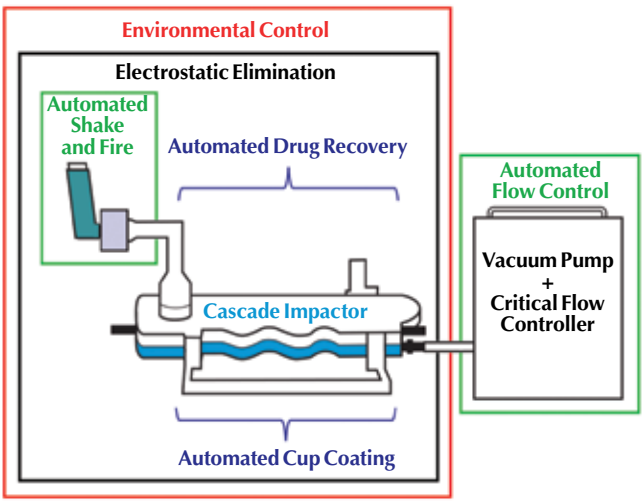
Flow control and flow rate (along with other flow-related parameters) are further examples of the potential for variability associated with test equipment. Setting and controlling air flow rate is essential to achieve defined, calibrated separation performance from a cascade impactor, and by extension, to measure an accurate APSD. This is clearly recognized in the pharmacopeias,[7,8] which specify that test flow rate should lie within ± 5% of the target flow (including errors associated with determining and setting flow), a margin that equates (via Stokes Law) to a variance in stage cut-off diameter of approximately ± 2.5%. Modern flow meters that use electronic flow control sensors offer important gains relative to traditional rotameters, within this context, delivering a degree of precision greater than ± 2%.

Flow control is especially important for DPIs, which, as passive devices, can see their aerodynamic performance significantly influenced by variation in flow rate. Here, integrated state-of-the-art critical flow control accessories can be helpful in reducing variability. These controllers automate many of the steps associated with determining and maintaining the precise test flow rate required, in accordance with pharmacopeial methods, as well as notifying the user if they fail to meet certain critical test conditions.

Alongside test equipment, the operator or analyst ("Man" in Figure 1) is the major source of variability in testing and this cause is where automated solutions can make the most difference. Operators may have different levels of skill, understanding and experience but can also make mistakes through fatigue or from lack of motivation/concentration due to the repetitive nature of the tasks. Automating some of the most routine aspects of testing can have a significant impact on day-to-day workflow. Giving an operator automation solutions for agitation or actuation tasks, for example, may eliminate multiple periods of tiring, uninteresting work throughout the day. The reduction in variability associated with automation of the specific tasks is therefore also likely to be accompanied by an overall improvement in motivation and the quality of work output. This improvement in measurement precision can be especially significant in product release testing, where errors can lead to failure of a batch to meet release specifications or, at a minimum, a long and costly investigation and impact analysis. Figure 2 illustrates how automated solutions sit alongside technology already discussed and shows additional solutions (such as those for electrostatic reduction) in a comprehensive variability reduction strategy, highlighting some of the tasks that are especially amenable to automation. These include the shaking and firing of MDIs, impactor cup coating—a process most often associated with the APSD measurement of DPIs—and the drug recovery processes associated with APSD measurement for all OIPs.

Figure 2

A schematic illustrating strategies for variability reduction, showing how modular automation solutions are applied alongside other accessories and practices.



Automation solutions: 1. Shaking and firing MDIs

The potential for the actuation technique of an analyst to impact drug delivery is highlighted by the pharmacopeial specification that "a mechanical means of actuating the pump assembly be employed to deliver doses for collection" when testing nasal sprays.[7] The majority of MDIs differ from their aqueous nasal spray counterparts with respect to the fact that they are propellant-driven. Pressing down on the canister seated in its actuator releases a metered, pressurized dose of liquid containing active ingredient(s), excipients (if present) and propellant into the mouthpiece. Exposure to ambient pressure triggers rapid expansion of the propellant, which vaporizes to disperse the solution- or suspension-based formulation to a respirable fraction. Complete refilling of the metering valve chamber is an essential prerequisite to a further successful actuation. While there are currently no pharmacopeial requirements for the

mechanical actuation of MDIs during testing, it is widely known that variability in the delivered dose can arise from the following causes:

- technique used to shake the device before actuation (shaking speed, angle and duration)
- magnitude of any delay between shaking and firing
- actuation force profile (force/time) applied
- length of time between repeat firings
- storage conditions during testing (orientation)

Shaking brings all the components of the MDI formulation into intimate contact, re-dispersing any suspended solids, which may cream or settle extremely rapidly, depending on the properties of the formulation. Actuation force profile and the length of time between repeat actuations can influence emptying and refilling of the metering valve chamber (the "priming" process that readies the inhaler for further use). Storage conditions, including temperature and orientation, have been directly linked with loss of prime and variability in drug delivery.[9, 10] Devices that automate the shaking and firing of MDIs can eliminate all such sources of variability with systems available for two discrete tasks: actuation to dose collection and actuation to waste.

DDU testing and APSD measurement require the actuation of a single MDI into a dose uniformity sampling apparatus (DUSA) or cascade impactor respectively, for assay. Single shake and fire stations meet this requirement, enabling the close control of shaking parameters and the applied force/time actuation profile. The most advanced systems offer mouthpiece adaptors for easy switching between products and incorporate an integrated air flow system to remove any requirement for additional ancillaries and vacuum pumps.

For multidose MDIs (and DPIs), there is an additional requirement to confirm DDU through container life, as well as from product to product. For example, current draft FDA guidance[11] recommends the measurement of nine samples, three at the beginning, three at the middle and three at the end. This creates a significant requirement for actuation of the inhaler to waste, with the regulatory expectation that this procedure will be carried out under representative conditions. Waste actuation can be carried out with a single product station, as described for dose collection. For instance, a fully automated shake and fire system can be coupled with a DUSA stack, a series of up to four DUSA and a waste shot collector, for walkaway DDU testing with samples automatically directed to the correct collection device (Figure 3).

The productivity of a single station can become limiting for certain tests and, as routine testing ramps up, into production. Consider the United States Pharmacopeia (USP) specification for dose uniformity over the entire unit life, which involves sampling ten MDIs, once at the beginning and once at the end; a total of 20 determinations with close to 1,000 shots to waste for testing a 100-dose inhaler.[12] With a single test station, it can take between one and three hours to actuate waste shots to get from the beginning to end of life samples, tying up the system for significant periods of time.[3] Ten-way, automated shake and fire testing systems directly address this issue. With these systems, design features that can be advantageous include:

- dedicated air flow and waste channels/collectors for each inhaler/can—this ensures that every inhaler is wasted under identical, well-defined conditions, matched to those used on a single shake and fire system where required. Subjecting each inhaler to an individually controlled, known air flow rate eases method transfer from a single shake and fire station and permits the reliable wasting of breath-actuated MDIs. Furthermore, for all MDIs, dedicated waste channels are associated with minimal cleaning and a reduced tendency to clogging, which means even high-volume products can be tested in a single run without blockage/interruption.
- individual force-to-actuate application—designs where actuation forces are applied individually to each inhaler, rather than averaged across all ten inhalers, offer more accurate, repeatable actuation, and again support the robust transfer of a method from a single station system.
- easy product changeover—inhalers are often tested in-actuator but can-only actuation to waste is common practice. The flexibility to do either type of testing, the ability to switch easily between the two, and between different commercial products, is beneficial and a major consideration for organizations offering contract testing or research.
- scale-up and reliability—the ability to apply/maintain the same shake and fire to waste

Figure 3

A single automated shake and fire system in combination with a DUSA stack and waste shot collector allows walkaway DDU testing of MDIs.

conditions on a ten-stage station as on a single stage system can be a significant advantage as a product moves through to commercialization. More generally, when investing in automated systems, well-engineered platforms that are easy to use can pay dividends in terms of high reliability, reduced maintenance and lower manual input, day-by-day. Such considerations are especially important for high throughput systems that will ultimately be relied on for QC.

Automation solutions: 2. Drug recovery

The rigorous recovery of drug from every potential deposition site within a cascade impaction set-up is the most manually intensive part of APSD measurement. This process is highly amenable to a step-by-step approach to automation, as illustrated in Figure 4. The left column shows the processes associated with manual drug recovery from an NGI; in the middle column certain rinsing and agitation tasks have been automated. Low-cost, labor-saving devices for routine tasks such as

Assessing the impact of automated actuation on MDI testing: An example

A comparative study carried out by researchers at Presspart Manufacturing Ltd (Blackburn, UK) illustrates the reduction in variability that can be gained from using automated shake and fire systems rather than manual actuation for MDI testing. For complete details of the study and all tests conditions, see reference 12.

Tables 1 and 2 show summary DDU and cascade impaction data measured for a salbutamol (albuterol) sulphate CFC-free inhaler (100 µg, IVAX Pharmaceuticals, Ireland). In a first set of tests, delivered dose was measured as a percent of label claim at the beginning, middle and end of product life, by three trained analysts, with all actuations, including firing to waste, performed manually. This set of tests was then repeated using an automated shake and fire system (Vertus® II, Copley Scientific, Nottingham, UK) for dose collection and an automated firing to waste unit (DecaVertus® II, Copley Scientific, Nottingham, UK). Similarly, cascade impaction measurements were made by two analysts using a Next Generation Impactor (NGI; Copley Scientific, Nottingham, UK), at the beginning and end of product life, first with all actuations performed manually and then using the automated systems. The results were reported in terms of mass balance (MB) and impactor sized mass (ISM) as specified in both pharmacopeial and FDA product-specific guidance for albuterol sulphate.[7,13]

Critical actuation parameters, such as force-to-actuate, inhaler shaking speed, shaking time and hold time, were kept constant across both automated actuation systems to ensure that the inhalers were fired to collection and waste under identical conditions. In addition, a short design of experiments (DoE) was carried out to establish a firing force to match the results generated by manual analysis.

The percent relative standard deviation (%RSD) associated with the combined delivered dose results for all three analysts, comprising over 90 readings in total, shows that the change to automation reduced variability; in terms of %RSD, from 8.8% to 7.5%. Similarly, the combined automated cascade impaction data for both analysts, comprising over 24 readings in total, also showed less variability. Here the RSD for the automated determination of MB was 8.2% rather than 9.3% and the corresponding RSD associated with the ISM determination decreased from 12.5% to 9.2%. These data highlight the clear and positive impact of the automated solution on the precision of the measured data. In terms of productivity, the automated testing took *approximately 30% less time* than the manual analysis and was recognized as a significant gain. In addition, the use of automation was associated with a substantially reduced training burden.

Table 1

Summary of comparative DDU test data measured by three analysts, manually and using automated shake and fire/wasting systems

Details	Ex-Device Dose (%)	% RSD
Between 3 analysts with automated shake and fire system	93.31	7.5
Between 3 analysts with manual actuation	94.37	8.8

(RSD is relative standard deviation)

Table 2

Summary of comparative cascade impaction test data measured by two analysts, manually and using automated shake and fire/wasting systems

Details	MB (%)	%RSD	ISM (mcg)	%RSD of ISM
Between 2 analysts with automated shake and fire system	88.91	8.2	54.01	9.2
Between 2 analysts with manual actuation	85.42	9.3	45.08	12.5

(MS is mass balance; RSD is relative standard deviation; ISM is impactor-sized mass)

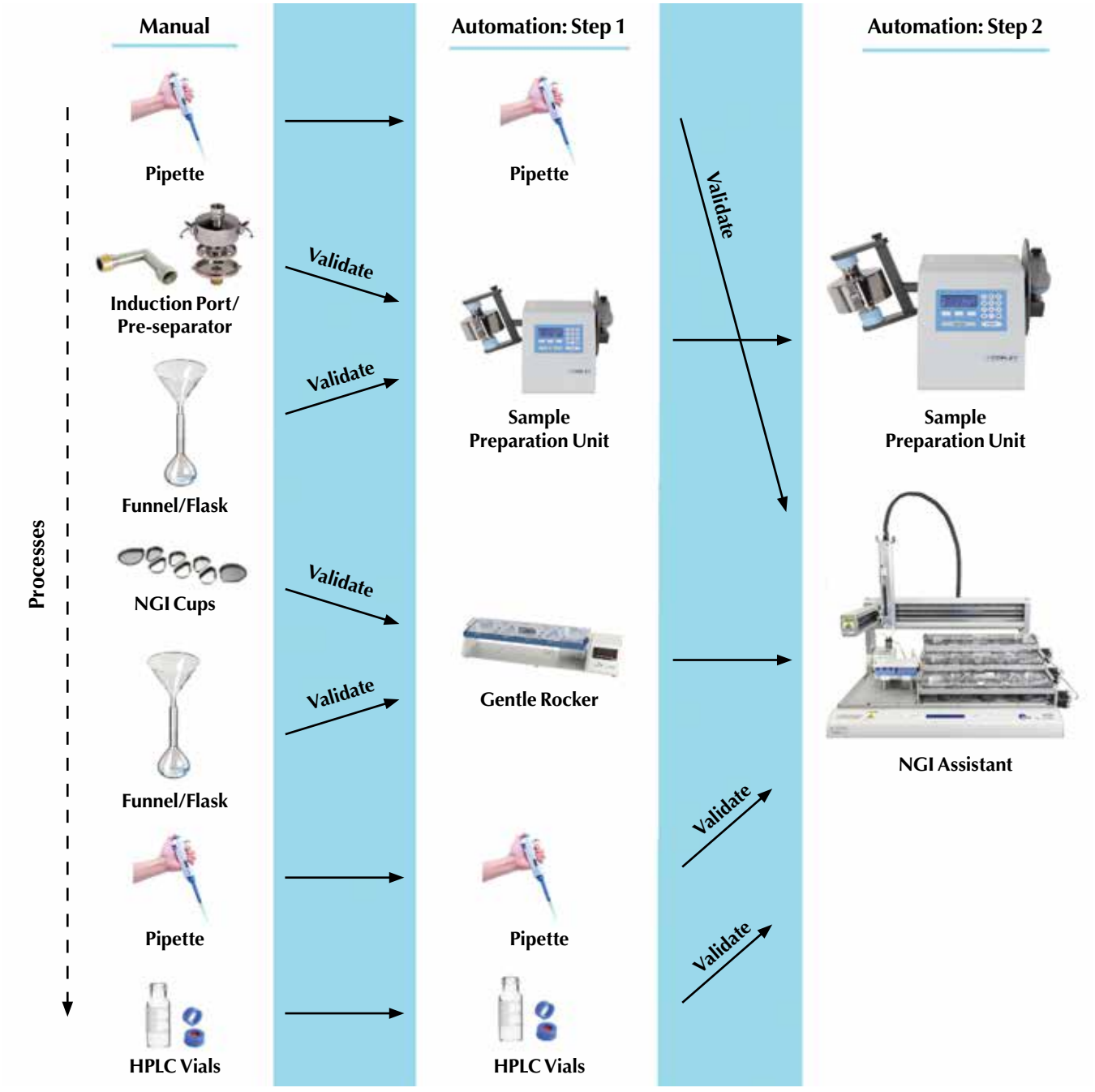
the rinsing of individual pieces of equipment (such as DUSAs, induction ports and/or pre-separators) and for agitating dispensed solvent in the cups of an NGI can ensure the consistent wetting of internal component surfaces, the application of a precisely defined agitation profile and completely reproducible drug recovery from a specific component/stage.

More complex, "load and go" systems that automate the complete drug recovery process are the final step in the semi-automation journey (Figure 4, right column). For example, an analyst can simply dismantle an NGI directly into an integrated, automated sample handing system, which accommodates up to three complete cup trays or a combination of cup trays and up to three Ph. Eur./USP induction ports or three pre-separators. Such systems automatically dispense the volume of solvent required to each component, apply a gentle rocking action to dissolve the active pharmaceutical ingredient (API) and extract primary and back-up samples, in industry standard HPLC (high pressure liquid chromatography) vials.

With this step-by-step approach, automation can be scaled up as the product progresses through its development milestones, without changing the underlying processes. Critically, even the most complex modular automation solutions are readily validated back to the entirely manual process, providing the reassurance of a straightforward switch-back should it be required. Integrated semi-automation solutions continue to evolve to offer quicker cycle times and higher produc-

Figure 4

A stepwise approach to automating discrete tasks, such as drug recovery from the NGI, can reduce the validation burden and risks associated with implementing progressively more advanced automation solutions.



tivity, and the potential for high returns/short payback times, particularly for the routine testing associated with QC. With a stepwise approach, these benefits can be accessed with minimal risk.

In conclusion

Reducing the variability associated with inhaler testing, notably cascade impaction testing, is a critical, ongoing activity for the industry. Experience suggests that the complete automation of testing is not always the best solution due to the complexity, risk and investment involved. Rather, best practice centers on semi-automation, the use of proven, modular, easy-to-validate automation solutions integrated within a wider variability reduction strategy. Such solutions not only reduce the variability associated with testing but, at the same time, increase analytical throughput, boosting operator morale and productivity. As a result, they can offer an attractive return on investment, alongside the much greater prize of substantially enhanced data quality and integrity.

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