Design of an inhaler-specific robotic system for laboratory use in early development

Challenges and opportunities to advance product development

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A set of trays giving access to 60 inhalers. In total, five similar racks can be program-selected, providing storage capacity for 300 devices.

Introduction

The complexity of current inhalation devices requires thorough testing of all aspects of device reliability. Classic manual testing constitutes an important part of the process, while for the sake of completeness, human factors engineering and usability studies address the variability introduced by the human user. However, as far as reproducibility is concerned, automation can provide strictly predefined handling at high throughput, which may be beneficial in obtaining the low variability required for the prediction of reliability, in view of expected failures in the low parts per million (ppm) range. However, depending on the specific situation, poorly-designed automated tests may miss important failure modes simply because of the deterministic way of testing.

This article addresses the challenges of automated testing in early development, where two additional concerns arise: 1) the need for fast adaptation of test equipment when shape factors change, which can happen often in early development and 2) the need for high throughput and reliable test results, which are ensured by lean qualification and validation procedures. In this article, robotic testing is presented as an additional voluntary effort during development of an innovative multi-dose inhaler, yet the compendial, conventional, manual release tests were still in place and carried out in compliance with all applicable regulations. The inhaler evaluated by this robotic system delivers liquid droplets from a non-pressurized reservoir. A spring-operated piston pump inside the inhaler meters the dose and generates the necessary pressure for atomization. Therefore, some aspects of the system are specific to this type of inhaler, However, many aspects of the robotic system will be applicable to other aerosol delivery devices.

General considerations for automated versus manual testing

Automated testing represents a considerable investment, not only in hardware but in labor. The expertise required to design an automated system calls for both technical and regulatory competence. Lead time is required if a new automation project is to be launched. Often the design of dedicated robotic test modules is time-consuming while qualification and validation activities can prohibit efficient use of automated test systems during early development. In comparison, manual tests may be started faster and can be more flexible. However, that quick-start advantage must be balanced with the unique reproducibility and speed of robotic tests, as well as the reduction in human labor, once a robotic system has been established. If time to market is the highest priority then manual tests are likely to be selected. Yet in that situation, testing specifications must consider future automation. Experience and an interdisciplinary team are required to enable optional automation at a later point in time. For example, if a delivered dose measurement were to be automated, the consumption of solvent might be lower if performed manually by experienced personnel. The (common) testing specification must be written with future automation in mind, in a way that man and machine can run the test. This exchangeability is the ultimate goal of automation. If an increased number of similar tests motivates large-scale automation for

Table 1

Comparison of manual testing versus automated testing

Issue	Manual Testing	Automated Testing
Frequency of similar tests in industry	Well established, see pharmacopeial chapters	Case by case, customer specific, device specific
Accessibility	Easy	High initial investment
Flexibility	High	Requires re-design (e.g., if handling or casing of device is changed)
Time to first test	Short	Follows design and realization of system
Reproducibility	Written operating instructions and training establish reproducibility	Sample handling is program controlled, sensors check execution of commands, mechanical backlash small in comparison with variability of human handling
Obtain specificity	Acquire instrumentation, create detailed instructions, training of analyst	Design of system, selection of sensors, mechanical construction, training of operator and technical support (service staff)
Regulatory status, quality	Training and check, qualification of instruments and validation of methods, humans introduce undefined variability	Best practice of design, standards, quality control of machines, software, data integrity, qualification and method validation, training of operators and service personnel
Environment	Laboratory climate control, humans are undefined sources of particles, heat and humidity	Robot housing is under climate control, environment is defined

release testing, the experiences of qualification and validation can be transferred and recycled when the needs of robotic testing have been considered in early development. Table 1 provides a comparison of manual and automated testing.

Capabilities of the present robotic system

A robotic system was developed by a Boehringer Ingelheim team to test the company's Respimat® Soft Mist™ inhaler (Figure 1). The system was designed to run more than 1,000 actuations per 24 hours and to perform specific checks concerning the operation of the inhaler. Among these are:

- Dose consistency (metered mass and delivered mass, which is a surrogate for the delivered dose, determined according to pharmacopeial procedures)
- Plume geometry of the active inhaler
- Particle size distribution (this capability was implemented after the robotic system was initially put into use)

Figure 1

A robotic system developed by Boehringer Ingelheim for early development testing of the Respimat Soft Mist inhaler

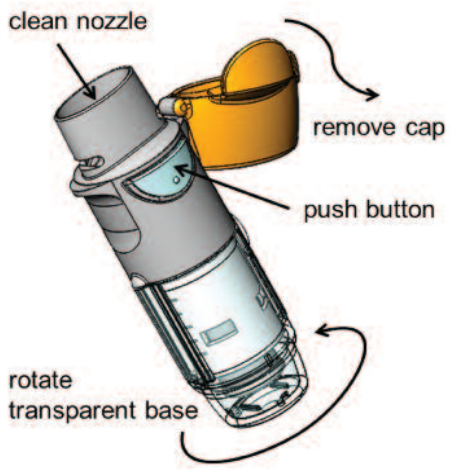
The handling tasks performed by the present robotic system are illustrated in Figure 2. Using the Respimat Soft Mist inhaler consists of gripping the device, rotating the transparent base, opening the cap and pushing the release button. After use, the cap is closed and the device is stored. In our robot, automated storage for 300 devices was available. Thereby, long-term investigations of once-daily dosing schemes could be envisioned.

Active devices like the Respimat Soft Mist inhaler or a pressurized metered dose inhaler (pMDI) are well-suited to be checked for plume geometry and laser particle size measurements. Dry powder inhalers (DPIs) would benefit from additional test modules that generate a defined air flow. Most DPIs will also require chemical analysis of the dose and/or particle size analysis by cascade impactors (which was not implemented here).

At present, operation of the device is checked by the test modules listed in Table 2. Measurements to be performed are entered in a Microsoft Access database prior to the start of the test series. A supervisor program interfaces the

Figure 2

Steps in testing the Respimat Soft Mist inhaler



robotic arm, the various test modules and their individual sensors, schedules the tests and enters the results in the database. On a daily basis, the content of the local Access database is automatically transferred to an Oracle database operated by the company's information technology service.

Table 2

Overview of operations to be performed by the automated testing system and implementation chosen

Action/Property	Component/Sensor Installed
Handling	6-axis robotic arm by Yaskawa (Japan), station tilting the device during preparation (rotation of base)
Apply and remove cap	Pneumatic gripper
Prepare inhaler/torque	Electric drive/torque sensor (Hottinger Baldwin, Darmstadt, Germany)
Press release button/force	Pneumatic cylinder/force sensor (Hottinger Baldwin, Darmstadt, Germany)
Detect sound (spray duration, empty device, mechanics ok?)	Sound meter (Brüel & Kjær, Nærum, Denmark)
Particle size distribution	Malvern Spraytec (Malvern, Worcestershire, UK)
Plume geometry	2 cameras, 90 degrees offset
Spray duration, spray front velocity	Camera @ 25 fps, corresponding to 40 ms time resolution
Weigh/delivered mass and metered mass	Balance (Mettler, Germany) and nozzle cleaner

Flexibility in robotic design is critical

The inhaler being tested was in early development and expected to undergo design modifications. Therefore, flexibility was a key focus in the robot's design and its modular capabilities directly result from this requirement. The robot incorporates the following components, also described in Table 2:

- 6-axis robotic arm: Due to space restrictions, sample transfer by 6-axis robotic arms was preferred. Linear transfer systems may be simpler but require more space.
- Capping station: For long term tests, the possible influence of the cap was considered and the inhaler was stored in a closed state.
- Preparation: Rotation of the transparent base was performed and the torque was measured.
- Release unit: Device release triggered cameras as well as laser diffraction (Malvern). The cameras provided images (25 frames per second) permitting measurement of spray duration and (optionally) spray front velocity and plume geometry.
- Balances: Equilibration of balances at a resolution better than 0.1 mg is time-consuming. Therefore, two balances were operated in parallel.
- Laser diffraction

Figure 3

The modules of the robot have inserts that account for changes of the device casing during development. A storage position (left) and the release position (right, with the Respimat inhaler and gripper) are shown.

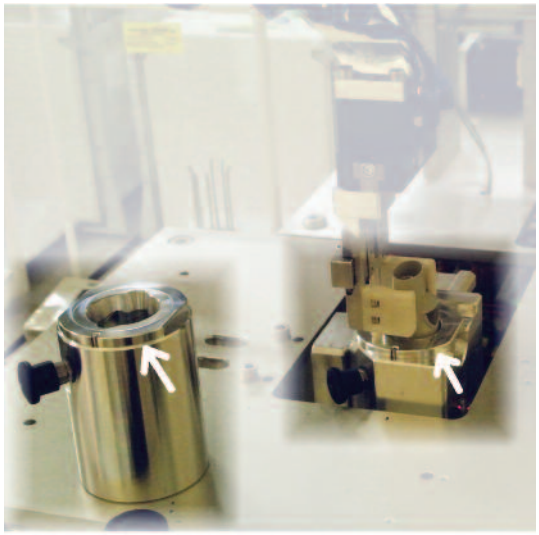


Figure 3 shows an example of the modular design of the sample interface. Inserts in the different stations allow for a quick change thereby enabling design modifications of the device under test. The gripper unit of the robotic arm was first designed using metal tweezers but later molded-fiber-enforced epoxy grippers were used. Finally, the grippers were made of three-dimensional rapid prototypes and provided such a good hold that spring-loaded, pre-determined breaking points were installed.

Due to the specific operation of the inhaler, laser diffraction could be applied for particle sizing. Depending on the inhaler and the formulation, this may not always be appropriate. For example, pressurized metered dose inhalers with their propellants would

require careful implementation. The refractive index of the propellant gas and utilization of a solution or a suspension pMDI require additional effort (in design and validation) if measurements are to be correlated to impactor measurements providing aerodynamic particle size distributions. There is a compromise between the way in which particle size measurements are performed and the measurement of plume geometry and plume velocity at the same time, because compendial methods rely on the EP/USP sample induction port.

Approaches taken by others

According to Weddle[1] the planning of an automated system like the one described here depends on three considerations: 1) interpretation of the United States Food and Drug Administration (US FDA) codes (Predicate rule), 2) environmental impact (risk) to the product and employees, and 3) a company's internal policies regarding information technology, security, safety, quality assurance or other mission-critical functions. These aspects have to be dealt with in detail before a robotic system can be designed.

We recommend a risk assessment that explicitly includes: 1) the FDA's likely view on the data to be generated[2] and compliance with quality assurance. In Europe, safety issues relating to workers, environment and information technology issues are taken into account by CE-marking the robot. The CE mark assures that the robot or its components were designed according to the relevant standards, including safety regulations.

In addition, the general acceptability of innovative methods must be scrutinized. The use of robotics might affect the conventional workload distribution between disciplines and departments in a company. When beginning development of a new inhaler, it must be decided early whether to opt for automated determinations of the delivered dose (DD) or delivered mass (DM) or even the particle size distribution (PSD), because only then can the testing specifications be developed, considering both man and machine.

The present robotic system is utilized in the early development process (non-GMP), therefore some overhead concerning cGMP documentation can be reduced to a minimum. However, gaining knowledge, applying it in production and then releasing inhalers is one of our goals.

The challenge is to implement robotic methods *within the cGMP environment,* then to propose suitable specifications and to transfer the sensor components to production where they can ultimately be used for process analytical technology (PAT). The application of robots in inhaler testing[3] and in the general pharmaceutical environment[4] has been documented in the past by leading companies. Considering the complex production process of the Respimat Soft Mist inhaler, DD, DM and PSD measurements are only possible after assembly and insertion of a cartridge containing either a drug solution or a suitable surrogate. This defines the possible position of these analytical technologies in the production process.

Figure 4

Commercially-available systems used in our laboratory include the ICTUS from Novi Systems.

Benchmarking

The robotic system described here is considered to be a technical feasibility study and not intended to be marketed. Currently, commercial solutions are available that provide either fully-automated particle size analysis based on the Andersen impactor[5] (Figure 4) or semi-automated recovery of the material deposited in the Next Generation Impactor (NGI).[6] While full automation requires customization, an NGI sample recovery system (SRS) (Figure 5) offers off-the-shelf, semi-automation that generates confidence in its serviceability and long-term availability, in part because it is not dedicated to one manufacturer or one device. This offers a likely positive return on investment, in spite of its demand for more manual labor per test. Further advances in laser diffraction however, may favor the robotic approach presented here.

In general, during inhaler testing, the most time-consuming test is the aerodynamic assessment of the particle size distribution. On average, four distributions per day are

Figure 5

An NGI sample recovery system used in our laboratory, from MSP Corporation

measured manually. Switching to surrogate techniques, the throughput is several tens of times that of existing, commercially-available robotic impactors, and hundreds of times that of fully-manual impactor use. However, work flow may be increased with existing commercial systems by utilizing fewer stages to gain speed, e.g., by using a two-stage impactor or the Alberta Idealized Throat plus filter or an abbreviated impactor. While the present system and one of the robots are fully automated and deliver either the data or vials ready for analysis, another automated system requires manual work, mainly the handling of the inhaler device. The speed of the present system relies on the use of surrogate parameters, e.g., delivered mass instead of delivered dose or the applicability of laser diffraction for particle size measurements instead of impactor work. The type of inhaler being tested will impact the testing methods available for simplification, as will acceptance by authorities who determine the success of this quickly developing field of test automation.

Conclusions

Automated testing is close to ideal for the investigation of consistency and reliability of inhalers and other devices. The robotic system presented here is mainly suited for development purposes because of its designed-in flexibility. Based on its data, inhaler design decisions can be made with greater certainty. As a next step, elements (e.g., modules) of this robot can be transferred to production and may be implemented as process analytical technology, where only a high throughput test system can provide the necessary testing robustness at an affordable cost.

Acknowledgements

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