



## H&T PRESSPART

# DOSE COUNTERS AND INDICATORS – MEETING A REAL PATIENT NEED

Providing methods for predicting the end of life of pressurised metered dose inhalers (pMDIs) and incorporating mobile Health (mHealth) technology would improve patient safety considerably. Inga Meyer, Global Business Development Manager, and Kyle Wilson, Technical Applications Engineer, from H&T Presspart, explain how their dose counter-enabled inhaler development work has led to the production of a system that accurately indicates the end of life of a device.

Asthma and chronic obstructive pulmonary disease (COPD) are chronic lung disorders responsible for millions of deaths every year. Both diseases are characterised by variable and recurring symptoms and when poorly controlled, can result in severe limitations in quality of life of patients. Controlling and monitoring treatments therefore is not only meeting a real need to reduce healthcare costs related to hospitalisations but a real patient need.

Patient expectations are for a reliable system to support their correct and timely use of inhalers, without changing the way of using them or adding any steps to their routine: devices need to be intuitive and non-destructive, without much additional weight or change in shape.

Furthermore, in addition to a safety system to help patients know about the filling status of their drug, they would like help with adherence and compliance. The majority of marketed metered dose inhalers (MDIs) offer no practical way for patients or doctors to know how many doses are left in their inhaler, specifically in case of emergency. Furthermore, there is a collective requirement to track adherence or compliance to medication.

To address these requirements, the US FDA published guidance on integration of dose-counting mechanisms into MDI

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drug products. Under this guidance, devices should offer either clear numeric counting mechanisms or indication functions with colour coding or other means, so patients have clear and unmistakable information on the amount of drug left in their devices.<sup>1,2</sup> The guidance also encourages drug manufacturers to update existing devices, if possible.

Pharmaceutical companies worldwide are working on integrating dose-counting or -indicating mechanisms into their pMDI to both address the patient need and differentiate their products in an increasingly competitive pMDI market space. Available solutions include mechanical and on-can dose counter and indicator systems, and an ever-increasing offering of connected counting and health management solutions.

H&T Presspart has a portfolio of counting and indicating solutions to address the variety of customer and market requirements and is actively supporting a number of global dose counter and indicator programmes for pharmaceutical clients in all types of counting projects (Figure 1).



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Figure 1: H&T Presspart's end of life indication product portfolio.

## INCREASED SAFETY, CONVENIENCE & DIFFERENTIATION

To address the transition towards indication of end of life of the device, H&T Presspart offers a mechanical dose-counting system, a licensed product design from 3M, which is suitable for any generic or new chemical entity (NCE) development and designed to be compatible with all marketed pMDI valves. It is supported by a variety of actuator styles and geometries meeting the performance and regulatory targets for any given formulation.

The dose counter technology was the first integrated dose counter available for third party developments and first to be approved by the FDA in conjunction with a pMDI product.

### Development Process

Central to the development process is an understanding of the final design requirements. Such requirements are dictated in part by the specific components and formulation selected as well as any local regulatory requirements, performance requirements of the final package e.g. aerodynamic particle size distribution (APSD) and spray pattern plume geometry (SPPG) or additional customer-specific requests for the product.

Also integral to any component manufactured by H&T Presspart is the

quality-by-design promise to avoid undercounting, which is accomplished by understanding the requirements such as general formulation characteristics and preferred component selection.

The remainder of the development process consists of three key activities:

- Valve characterisation
- Actuator customisation (including colour and geometry selection)
- Robustness testing.

Valve characterisation starts with an assessment of the customer-selected valve on crimped and filled canisters. The data generated in this characterisation is used to confirm, or modify as necessary, the overall design in order to avoid undercounting.

Next, the final actuator is ready to be customised. Most important is perhaps the geometry selection process, especially when addressing generics programmes where APSD and SPPG measurements must match the originator. In these cases, factors such as the components selected or measuring equipment may have an impact, for which the geometry selection process can compensate, ultimately ensuring the performance requirements are fulfilled. In parallel, any other preferences are addressed such as colour selection for the body and dust cap as well as any embossing or other customisations desired.

Finally, the product is put through robustness testing. Such testing ensures the full package will withstand the rigour of regular patient use, proving that the design goals were fulfilled. Testing includes, but is not limited to, verification of through-life counting and drop testing and is performed on the full final assembly. The data generated from these activities will then be summarised for submission purposes.

## FLUTICASONE – A CASE STUDY OF DEVICE DEVELOPMENT

H&T Presspart has gained invaluable experience in the process of dose counter-enabled inhaler product development and brings this experience to the table with each new development program. Whether through the activities mentioned above or further activities on offer through our Inhalation Product Technology Center (IPTC) Laboratory, we are prepared to support any pMDI program. This is particularly important in the case of generics programs for the US market (Figure 2).

The complexity involved in preparing a generic for the US market is perhaps best illustrated by examining a representative scenario – the development of a generic fluticasone propionate product with an integrated dose counter. Filing into the US will require *in vitro*, PK and PD equivalence. *In vitro* equivalence can, in turn, be broken



Figure 2: H&T Presspart's Inhalation Product Technology Centre (IPTC) laboratory in the UK.

down into APSD, SPPG, and delivered dose uniformity parameters, all of which must be equivalent for success.

#### Finalising Dimensions & Target Specifications

The first steps involve finalising the dimensions required as a starting point as well as populating the data for the Reference Listed Drug (RLD) products to establish target specifications. Sourced fluticasone propionate RLD is tomography scanned for overall dimensions as well as critical internal dimensions such as orifice diameter, jet length and sump volume and to establish

target specifications via measurements on cascade impactors and laser imaging. In parallel, measurements are taken on placebo canisters with the selected valve as a part of a valve compatibility study. The customer-specific product is developed using the RLD geometries as a starting point.

#### Design of Experiments

To account for the influence of any differences introduced by the specific parts and formulation selected and developed by the customer, a design of experiments (DoE) is established. This DoE focuses on key dimensions of interest as agreed between

H&T Presspart and the customer and also utilises the rapid prototyping and testing capabilities available at IPTC. In this case, two actuators passing the initial screening are finalised and analysed by the customer for confirmation of best fit.

#### Robustness Testing

In parallel, all other actuator development activities are progressed to ensure colours and other design criteria are met. The design frozen product is run through robustness testing to ensure the final product is consistent with design expectation, namely a design that avoids undercounts, and is ready for filing to the FDA. All necessary data and documentation support is provided by H&T Presspart.

The process outlined above has progressed in a manner that ensures that the final design is robust, will count as expected, and is optimised in terms of *in vitro* performance characteristics. Further, use of a DoE to establish and test the design space has helped avoid costly and time-consuming sequential iterations. The final product is ready for filing with full confidence by means of supporting data.

H&T Presspart mechanical dose counters and indicators are available for generic and NCE formulations and our programmes support pharmaceutical customers from early stage development through scale-up, market launch and high volume commercial supply.

#### DEVELOPMENT OF QUANTUM

Pharma companies in less regulated markets are looking at ways to differentiate their offer and improve treatment outcomes without adding prohibitive cost to the package. To address those needs, H&T Presspart has developed the first on-can, cost-effective, off-the-shelf dose indication system marketed as Quantum™.<sup>3,4</sup> It provides patients with a simple but intuitive way to indicate that the pMDI canister is coming to its end of life and provides added convenience for patients such as treatment monitoring and compliance management via an optional mobile phone application.

#### How Quantum Works

The patient has to simply remove the can from its actuator, roll it on a flat surface and read an indicator arrow on the bottom of the can. Thanks to the on-can integrated bias weight, the canister will balance and indicate the remaining drug left in the

can. Compared with other dose indication systems, there is no change to the actuator required and no additional part in the flow path of the device.

Another key advantage is that Quantum always reads what is left in the can even if there is a slowly leaking can, for example. Through rigorous analytical and robustness studies in our labs, a dose-to-arrow angle profile has been developed that provides the basis for reliable feedback to the patient about the remaining fill level in the can and when the pMDI needs to be replaced (Figure 3).

#### User Study

To understand usage of pMDIs by nurses and asthma and COPD patients further as well as how Quantum can improve inhaler experience and patient safety, H&T Presspart conducted a user study with a group of 50 participants. In particular, the group was asked how they currently estimate the fill volume of their pMDI can.

Results showed that more than half of respondents simply shake the can to determine if it is empty. The study also showed that patients consistently used pMDIs until no more “puffs” occurred, which could lead to dangerous, potentially life-threatening situations in the event the pMDI turns out to be empty during exacerbations. And this fear was confirmed by the respondents as more than two thirds of patients said they were concerned with their current method.

During the study, participants were asked to estimate the current fill level of a pMDI can by shaking the can to estimate the can fill and alternatively using Quantum to evaluate the fill level. The response given was coded as a “success”, a “safe failure” or an “unsafe failure”. An unsafe failure occurs when the can is actually empty and the patient believes it is still safe to use or near empty.

Not surprisingly, the study demonstrated a high unsafe failure rate, confirming the unreliability of determining the remaining fill by simply shaking the can. The high unsafe failure rate dropped

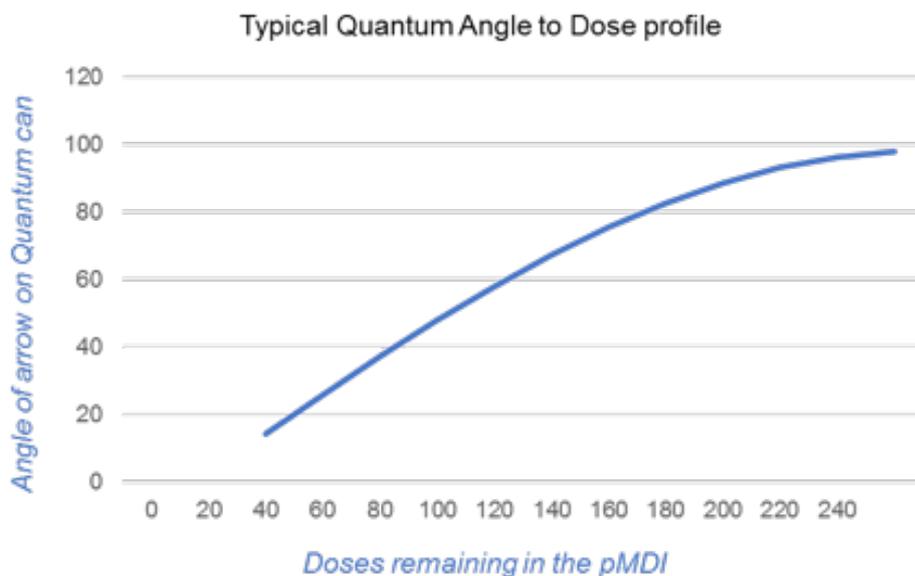


Figure 3: Typical profile dose/angle profile for a 200 dose pMDI.

significantly when the respondents used the Quantum dose indicator to make the decision about the fill level of the can. We could also demonstrate that there was potential for a further decrease of unsafe failures when Quantum was used several times supporting the effectiveness of the system after some initial training compared with simple shaking. Over 80% of participants found Quantum easy and effective to use.

#### Mobile Connectivity

To enhance asthma and COPD treatment management and patient compliance, Quantum has the option to connect to a mobile phone app which provides instant feedback to the patient on the medication left inside the canister.

The mobile phone app also incorporates adherence and usage-tracking features, reports, dose reminders for multiple medications, prescription re-order reminders, interactive training videos, patient information leaflets and the opportunity to integrate a variety of push notifications to patients. The app can be connected to cloud services to provide pharmaceutical companies, doctors and other stakeholders access to patient and medication data in real time to improve treatment outcomes and optimise the supply chain (Figure 4).

Quantum is applicable to all pMDI products independent of the number of doses. It can be used with all marketed valves and standard actuators and is easily implemented to a pMDI with no additional development time.

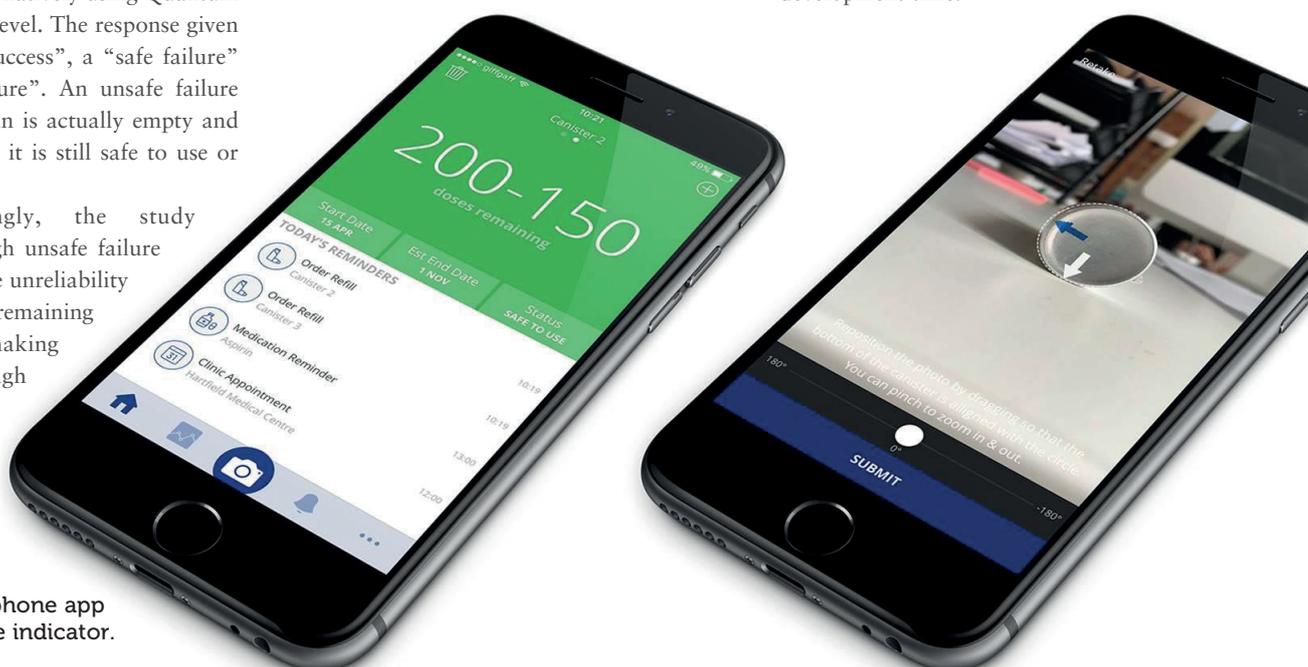


Figure 4: Mobile phone app for Quantum dose indicator.

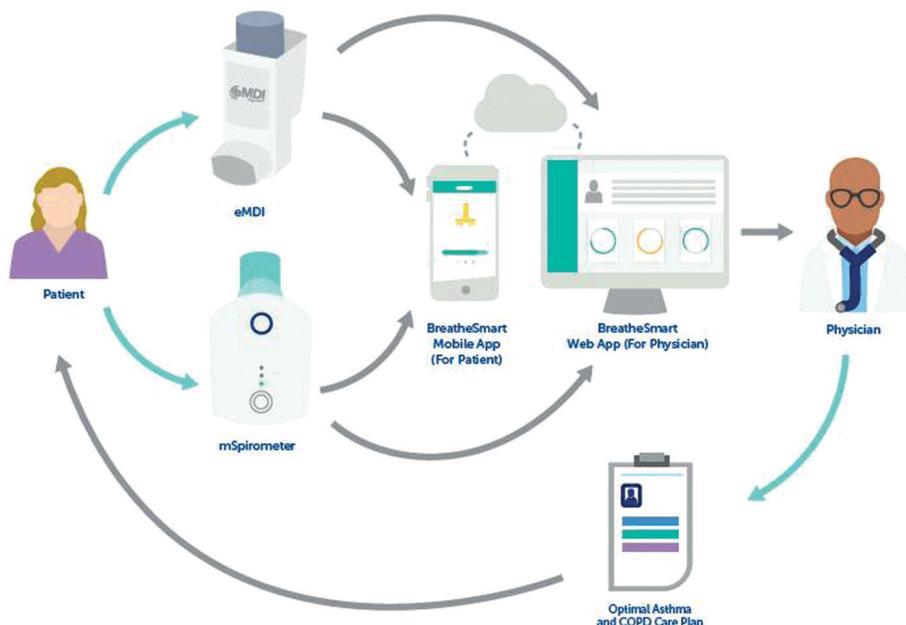


Figure 5: Integration of the eMDI with BreatheSmart in treatment management.

### CONNECTED DOSE COUNTING & MHEALTH SOLUTIONS

The increasing development of mobile health solutions on the market<sup>5</sup> has developed one area of focus on solutions for patients with asthma and COPD.<sup>6,7</sup> Over the years, a number of embedded and non-embedded solutions for pMDIs have been presented and/or officially launched to market, many of which have a history of use in clinical environments.

Developments of fully embedded solutions are designed to meet, firstly, the requirements of patients, but also address needs of physicians, health institutions, pharmaceutical companies and payers.

In 2013, H&T Presspart embarked on a strategic development programme focused on real-time pMDI patient data capture and transmission in order to address the requirement of patients and other key stakeholders within the healthcare sector. In 2015, H&T Presspart initiated collaboration with Cohero Health, a digital health company, to bring innovative device

and software tools and technologies to improve respiratory care, reduce avoidable costs and optimise medication utilisation.

In December 2016, H&T Presspart and Cohero Health launched the first market-ready, intuitive, fully embedded and connected metered dose inhaler, eMDI™ aimed at improving adherence and enabling continually optimised care of patients with asthma and COPD. The eMDI strongly builds on the existing design of pMDIs, to facilitate intuitive patient operation and ease of manufacturing.

One design option incorporates an FDA-approved mechanical dose counter which allows for quick integration into existing marketed drugs and supports a fast-track approval process for highly regulated markets. The eMDI is the only embedded device solution which integrates seamlessly with BreatheSmart from Cohero Health, a comprehensive respiratory disease management platform that uniquely enables tracking of both controller and rescue medications, along with clinically accurate lung function measurement, in real time (Figure 5).

By tracking, recording and sharing data on the use of both preventer (controller) and reliever (rescue) medications, the eMDI engages and empowers patients in their self-care, leading to improved adherence, while enabling real-time monitoring of medication use and symptom flare-ups by caregivers and the healthcare community. Medication utilisation data from the eMDI can be merged in real-time with lung function data from Cohero Health's mSpirometer – a clinical grade handheld wireless spirometer that precisely measures critical lung function metrics. This allows, for the first time, for the effects of preventer and rescue medication use on lung function to be tracked and analysed.

H&T Presspart is actively working with pharmaceutical companies to make the eMDI available to patient populations for daily treatment management in the near future.

### CONCLUSION

With a number of different solutions on the shelf at H&T Presspart and strong background in running programs for drug approval and large volume industrialisation, it is now in the hands of pharmaceutical manufacturers to pick the best solution for their product/market requirement and offer patients additional support in drug adherence and compliance.

### REFERENCES AND NOTES

1. FDA, *Guidance for Industry, "Integration of Dose-Counting Mechanisms into MDI Drug Products"*, 2003, p 1.
2. FDA, *Jurisdictional Update, "Metered Dose Inhalers, Spacers and Other Accessories"*, 2016
3. *Technology is licensed from Trig 1*
4. *Quantum logo is a registered trademark of Presspart Manufacturing Limited*
5. Monroe N, "Connected Combination Products: Past, Present & Future", *ONdrugDelivery*, 68 pp 5.
6. Asthma UK, "Real-world implementation of connected devices in the UK to reduce asthma attacks", pp 4
7. *Fortune.com, "Inhaler Makers Want to Watch Every Breath You Take"*, July 20, 2016.

## ABOUT H&T PRESSPART

H&T Presspart offers pharmaceutical customers high-precision injection moulded plastic components and deep drawn metal cans for respiratory drug delivery systems, with more than 40 years' experience and a worldwide reputation for competence, quality and innovation in pharmaceutical and industrial sectors. H&T Presspart's Inhalation Product Technology Centre (IPTC) supports new product developments and strategic initiatives with its customers. Founded in 1970 and acquired by the Heitkamp and Thumann group in 2002, H&T Presspart has three European manufacturing sites in Germany, Spain and the UK, with Sales offices in China, India, South America and the US.