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Designing a DPI for multiple constituencies

How a team designed a dry powder inhaler to meet regulatory requirements and cost restrictions while incorporating patient-friendly features

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Too often, after pharmaceutical companies spend millions of dollars designing dry powder inhalers (DPIs) to ensure that the products meet all regulatory requirements for consistent dose delivery, patient non-compliance and misuse negates the effort [1, 2]. Patients who can't fit their inhalers in their pockets may simply leave them at home, where the DPIs do no good at all. Other patients misunderstand the operation of a device, thinking for example, that they should hold in a button while inhaling, thereby preventing withdrawal of a capsule-piercing mechanism and preventing inhalation of the dose.

Designing a simple, easy-to-use DPI that also satisfies the needs of regulators and manufacturers presents a major challenge because solutions that satisfy one constituency often clash with solutions that satisfy the other. For example, a breath activated passive device may make coordination of inhalation and activation easier for the patient, but the inspiratory effort applied may result in inconsistent aerosolization, making it more difficult for manufacturers to demonstrate consistent dose delivery.

3M Drug Delivery Systems recently took on the challenge of designing a DPI that meets the competing needs of both pharmaceutical companies and patients. In the process, the team elicited some surprising information from patients and discovered innovative uses for technologies that had never before been applied to inhaler design.

Determining patient needs

Because the first step in meeting patient needs is to understand those needs thoroughly, the design team conducted a series of one-on-one interviews in the UK, US, and Italy. Patients interviewed represented all of the main FDA patient groups—the elderly, adults, and children—and had been using both prevention and reliever medications for at least two years.

The patients kept diaries for a week in order to record their inhaler use in real-life settings. The researchers also provided them with cameras to capture significant issues to do with use, storage, and other areas of particular concern. Device designers and experienced researchers then met with the patients and, in the case of children, their parents, to discuss key points identified from the diaries and to introduce a variety of other inhaler devices, including an early prototype of the 3M Taper DPI.

Researchers also conducted a number of interviews with specialist respiratory nurses in the UK who had responsibilities for training other respiratory nurses while still maintaining patient contact through pri-

mary care. The discussions focused on attributes that enable nurses and patients to recognize intuitively the steps necessary for the use of a device and other drivers that nurses and prescribers must consider when selecting an inhaler for a patient.

The patient study yielded some unexpected results. While the design team expected patients to emphasize the importance of compact devices that can fit into a woman's purse, they found that men actually had greater concerns about compactness since they often carry inhalers in their jeans pockets. Patients also expressed a dislike for model devices they deemed *too* small, explaining that they found very small devices difficult to manipulate.

Another revealing patient request occurred during a discussion of feedback indicators. On the whole, both patients and nurses expressed a desire for an indication that a dose has been delivered since DPIs lack the sensory clues inherent in the use of metered dose inhalers. On the other hand, patients did not want an indication, such as a very loud audible click, that might draw attention to their use of an inhaler. One woman interviewed, for example, specified that she would like to be able to use her inhaler in the cinema without embarrassment.

Determining pharmaceutical company needs

3M also conducted an e-survey with targeted respondents in the pharmaceutical industry. Unsurprisingly, the survey found that the primary expectations for inhalation devices involved cost and pharmaceutical performance measures, particularly efficiency and dose consistency. The pharmaceutical companies considered factors like ease of use secondary to performance expectations and rated the overall design of the device as a much lower priority than did patients.

The relationship between formulation and device

Early on, the 3M team realized that a device capable of delivering pure API would provide benefits for both patients and manufacturers. Using only micronized API without a lactose carrier could enable design of a more compact device, would likely reduce quality and risk issues, and would eliminate a number of manufacturing costs associated with purchasing, storing, and blending the lactose. Also, eliminating the need to detach the drug from a carrier would result in an extremely high fine particle fraction of the aerosolized formulation.

The bulk added to formulations by lactose carriers simplifies handling and dosing, but that bulk also may add to the size of delivery devices, especially those that use multiple capsules or blisters. Not only must the DPI have room to accommodate capsules or blisters, it also must be large enough to accommodate a capsule- or blister-opening mechanism. Both the physical size requirements for such a mechanism and the restrictions of the intellectual property landscape limit the possibilities for designing a compact DPI using capsules, blisters, or cartridges.

Novel uses of existing technology

While recent improvements in dosing have allowed for development of some pure API formulations, the vast majority of those products still require packaging the drug in capsules or blisters. With access to all of 3M's core technologies and experts from across the company's wide-ranging business segments, the 3M DDS team explored innovative ways to package and meter API for delivery of a large number of doses from a device with excellent performance. The team found the answer in two of 3M's major industrial capabilities: tape handling and microreplication.

The company has been manufacturing tape since 1925 and makes hundreds of different varieties for home, office, industrial, and health applications. Another of 3M's core technologies, microreplication, involves the use of tiny, precisely-shaped structures to give materials new physical, chemical, or optical properties. 3M successfully uses microreplication applications for applications ranging from light-enhancing film for laptop computer screens to mechanical fasteners. Minute pyramids make structured abrasives work better and wear more evenly, while microreplicated prisms in road signs, electronic displays, and exterior building illumination capture and reflect light.

Applying these technologies to the problem of delivering dry powder APIs for inhalation, the team designed a system in which microreplication and extrusion technology creates a carrier tape with hundreds of precisely-shaped indentations filled with pure active pharmaceutical ingredient (API). The number and spacing of the indentations controls the dose size, and the high van der Waals forces of the micronized API hold the powder in place. The coated tape, which can hold up to 120 pre-metered doses, is wound tightly on a spool, helping to prevent accidental discharge of the powder and allowing for compact storage within the delivery device.

Meeting patient and performance requirements

A combination of passive and active mechanisms helps patients coordinate their inhalation with aerosolization and reduces the flow rate dependence of the device performance. Releasing the API from the in-

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Figure 1

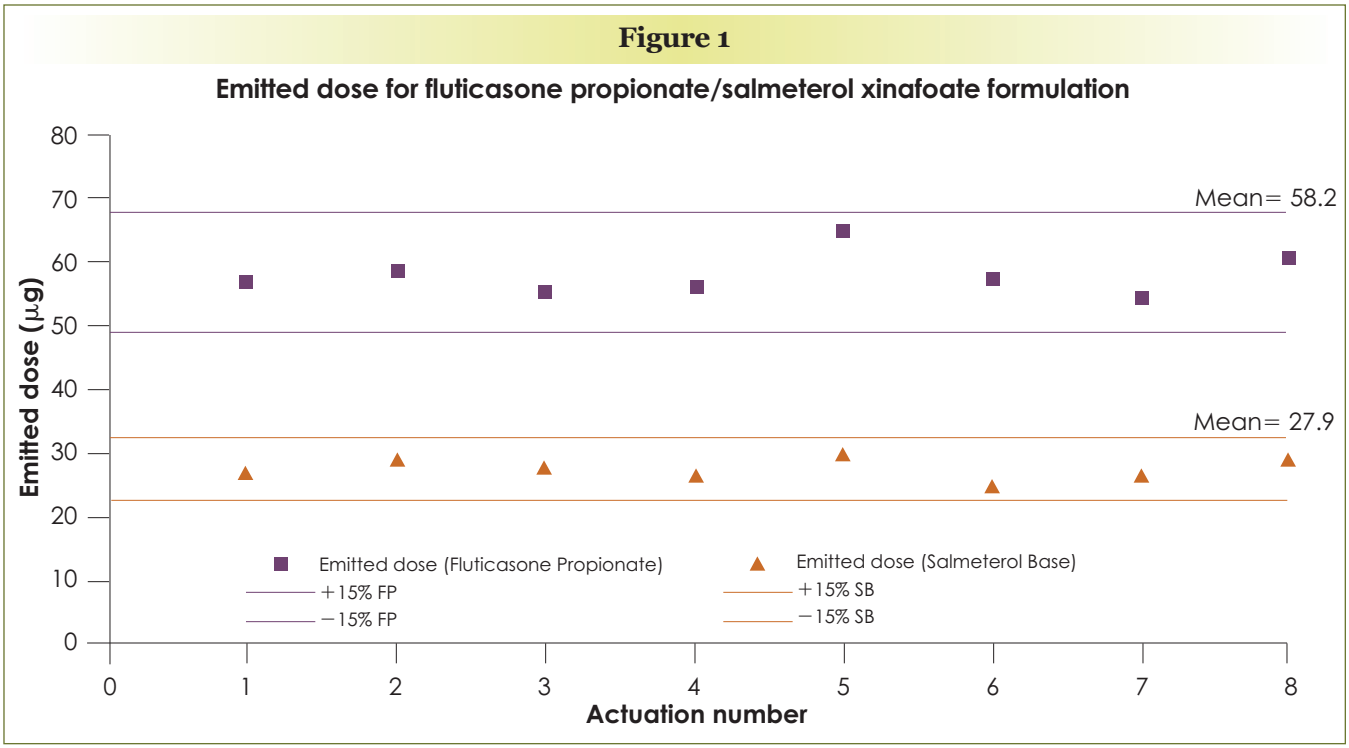


Figure 2

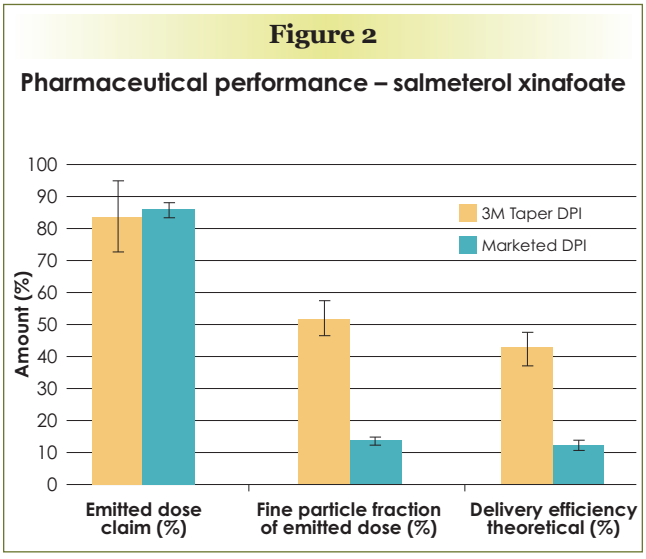
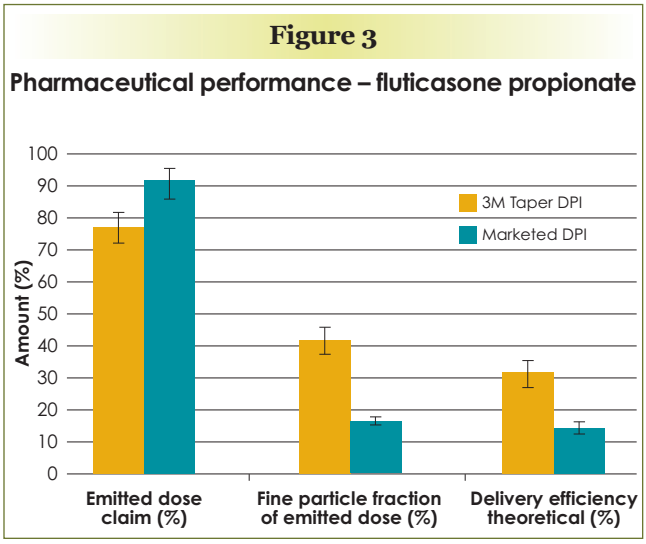


Figure 3



dentations and aerosolizing the drug requires imparting a significant amount of energy to the tape, in this case provided by a spring-loaded impactor that sets when the patient opens the mouthpiece cover. The patient's inhalation then triggers the release of the impactor, which strikes the tape and releases the powder.

In response to the surveyed patients' and carers' expressed desires for feedback from the device to indicate that the patient has taken the dose, the new DPI includes a ready-indicator feature in addition to a dose counter. When the patient opens the mouthpiece, setting the impactor and advancing the tape so that a dose moves into place for aerosolization, the device displays a green indicator to show that the inhaler is ready to use. As an inhalation triggers the impactor, the mechanism provides an audible click, and the indicator turns red.

The active mechanism assists with aerosolization and, in combination with moisture protection features, helps to ensure the pharmaceutical performance of the device, which has demonstrated an ability to deliver repeatable doses of pure API formulations such as a blend of fluticasone proprionate and salmeterol xinafoate (Fig. 1) with delivery efficiencies more than double that of a currently marketed device (Figs. 2 and 3). Tests with micronized albuterol sulfate showed that the device was able to deliver fine particle fractions of 65% consistently across the entire 120 doses stored in the device (Fig. 4).

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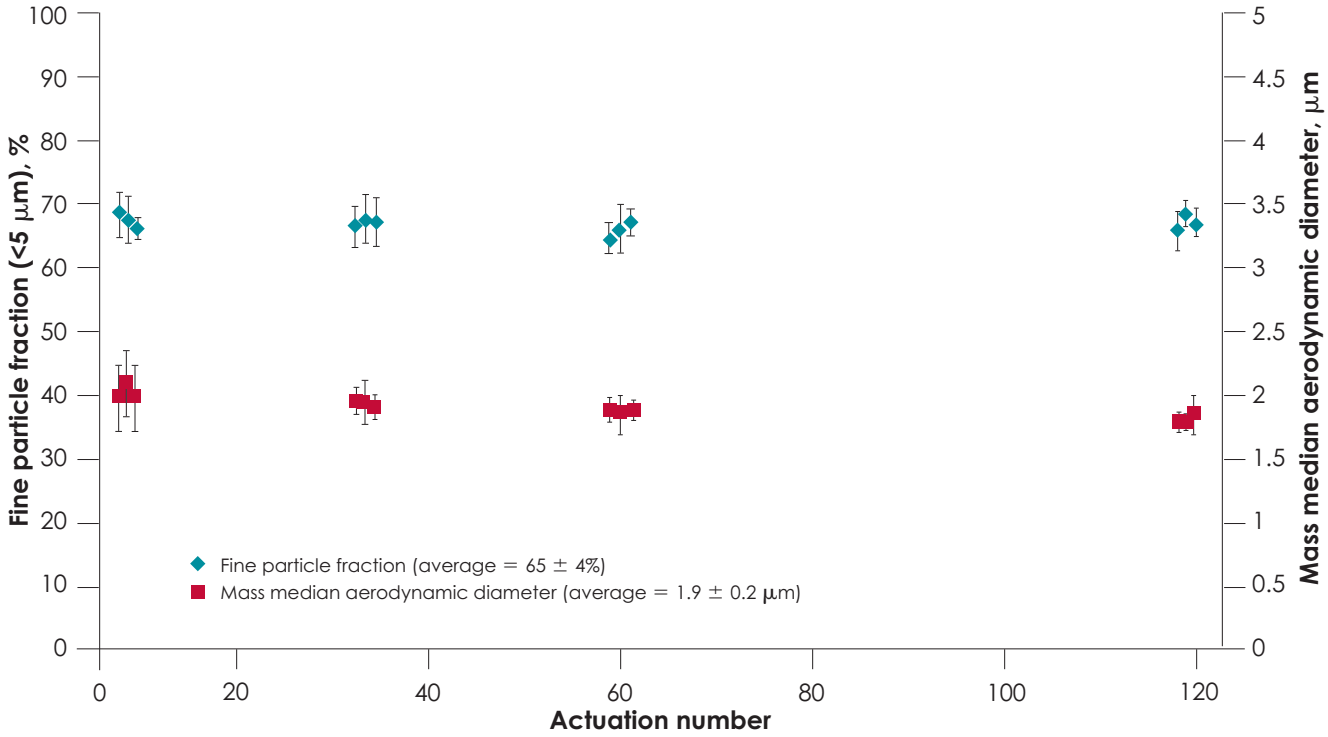
Figure 4



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