MEETING FUTURE NEEDS FOR RESPIRATORY DRUG DELIVERY DEVELOPMENT

There's a lot of work going into developing smart devices at the moment, but few examples of smart devices getting to the stage where they can be launched on the market. In this article, Mark Knowles, Head of Product Engineering, and Collette Johnson, Alliance Manager, both of Bespak, explore the different elements that need to be considered when developing a smart inhalation drug delivery device to ensure that maximum benefit is obtained.

Currently, there are around 300 million asthma and chronic obstructive pulmonary disease (COPD) sufferers that rely on inhalation devices for effective delivery of their medication.[1] However, using an inhaler is not easy – it takes skill and practice, whatever the design of the device, to ensure that inhalation and device actuation is synchronised, allowing the correct dose to be taken. To date, the focus has been on the medications, the device design and optimising how both work together in the hands of the patients, who themselves are a diverse and varied group.

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GETTING COMPLEX DEVICES RIGHT

Any drug and drug delivery mechanism should always start with the patient's needs in mind – and getting the device right first time is everyone's goal. To achieve this, establishing a multidisciplinary team from the outset is vital. However, inhalation devices in particular are extremely difficult to develop, and there is a storied history of failures for novel drugs and generics.

Device experts, like ourselves, have partnered with drug developers over the years to produce essential inhalation devices – we started work with Beecham (now GSK) in Worthing, UK, on Ventolin inhalers in the mid 1960s. Since then, innovation has driven the creation of many new technologies including metered dose inhalers (MDIs) and the introduction of dry powder inhalers (DPIs) (Figure 1). Nowadays, Bespak manufactures over 500 million inhalers per year (Figures 2 and 3).

Figure 1: Chiesi NEXThaler®, a multi-dose metered dry powder inhaler.

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Figure 2: Integrated dose-counting actuator devices in testing.

PROBLEMS WITH INHALER USE

Fundamentally, inhalers need to be intuitive devices that can be easily operated with simple or no instructions. As an industry, we are always trying to meet the challenge of right drug, right time, right amount. Although significant resources are going into educating patients and their families on how to use inhalers properly, such as ensuring breathing and actuation are correctly timed, there remains a significant amount of misuse. Shockingly, data shows that 76–94% of inhaler users are not using their devices correctly[2] and around 60% do not always take their medication.[3]

Typically, the correct breathing pattern for a standard inhaler is to breathe in slowly for around six seconds, with a force of around 30 N, and then hold your breath for about six seconds to maximise drug intake. Realistically, patients very rarely achieve this, but correct usage would potentially drive up yield significantly. Unfortunately, there are a number of asthma-related deaths that might have been prevented if patients were taking their medication regularly and properly.[4]

Figure 3: High-volume manufacture of dry powder inhalers.

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HOW CAN SMART INHALERS HELP?

Assessing Value

When it comes to smart technology and connected health, we need to assess what benefits it brings, particularly for patients, and be realistic about what it cannot deliver. At the moment, smart inhalers can determine if a device has been actuated, thus it is able to provide feedback on frequency of use. But the technology has not yet been developed such that it can say how much of the drug has entered the lung and, until

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there is some flow detection in the device, it wouldn't even be able to say if the drug had entered the lung in the first place.

So if smart inhalers at present can't solve this clinical problem, it's difficult to justify a significant increase in the device cost through the addition of electronics into a standard asthma inhaler. However, if you look at biologics, drug addiction therapy or pain relief, which are an order of magnitude more expensive than asthmatic drugs, then the economics shift. Additionally we can also start thinking about the value of secure devices where only a specific user will be able to administer a particular drug, for example in drug addiction therapy.

Smart devices could provide us with data and usage patterns, but will that information be valuable? Not just valuable to the pharmaceutical company, but ultimately for patients because, if they don't see the value, they won't understand the importance of using the device properly.

Making Devices Attractive

Smart devices need to fit into people's lifestyles and habits so that they can carry on with their lives without their condition drastically impacting it. Although we have made significant advances to tailor devices for specific patient groups and their carers, we need to go beyond that. Can we make devices more attractive for the user so that they actually want to use their device?

When designing devices we also need to look at the target demographic. For example, with children there can certainly be a stigma surrounding taking inhalers and being labelled a "sick" child at school, which may discourage use at the expense of their health.

For primary school children, ordinarily the responsibility lies with the teacher to ensure that they take their medication properly. But for high school children, the responsibility is more with the child so we need to do more both to help them better understand the impact of not correctly taking their medicine, and consider how to make the device more attractive to them in general. Perhaps we should be doing more to make inhalers customisable, enabling children to choose, for example, a suitable reward system for using their device correctly so that the device is perceived as having more "fun" elements by the user.

Harnessing Connectivity

With the rise of wearable devices and activity tracking, could smart devices be tethered to a mobile phone through a specifically designed app? If patients were not using the device correctly or had forgotten to take their medication, could this information be gathered and fed back to improve usage or set off a reminder for the user?

Smart devices could perhaps be used to provide information about user habits and the local environment, and potentially help us better understand an individual's condition. If location, air pollution and usage data could all be recorded, there may be observable usage patterns that would have otherwise gone undetected and measures could be put in place to manage their condition. For example, synthetic fertilisers can cause COPD patients to have severe exacerbations. Could we put sensors in a smart device for COPD users that maps the environment, or has an alarm that is activated when synthetic fertilisers are detected?

Then comes the challenge of implementing connectivity – how do we want the device to be connected (GPS, WiFi, Bluetooth) and how important would it be to be connected all the time versus potentially being offline and updating the app occasionally?

What about patients where connectivity just simply won't work for them? We have to remember that connectivity isn't going to be for everyone so, as we advance with connected devices, there still need to be adequate solutions for those whose devices, for whatever reason, are not connected.

Using Biometrics to Improve Security

Safe delivery of the correct drug to the correct individual is a challenge where connected devices and biometrics could potentially help. If something like fingerprint technology was included, it would shift capability beyond a simple Bluetooth device that is basically set with a defined inventory that says whether or not the inhaler has been taken, to then enabling safety lock-outs, child lock-outs and others. The right type of smart device could also be a powerful tool to help address drug misuse problems.

The challenge is that fingerprint technology is relatively expensive and so raises questions of cost-effectiveness. A whole layer of fingerprint verification decision making would have to be added in, which increases complexity both mechanically and on a software level.

SOCIO-ENVIRONMENTAL & ENVIRONMENTAL RESPONSIBILITIES

There are also socio-environmental and environmental factors to consider. Reducing plastics is a hot topic at the moment, and where we can, we are developing devices where certain elements can be replaced rather than needing to replace the whole device.

In terms of replacement, there are two types of multi-dose delivery devices: ones with an interchangeable add-on and ones where the whole device needs to be replaced once all the drug has been used. A large amount of plastic would be saved if we just shipped drug canisters alone, rather than the canisters and actuators.

However, shifting from a completely disposable device to an interchangeable one can be a challenge for patients, as it may take some time to use the new system correctly, i.e. remembering to only replace the add-on and not throw away the whole device. Proper education is therefore important but there could be a mechanism in the smart device that reminds the user not to throw the device away.

In addition, we need to consider correct disposal of the various parts. Smart devices that use battery technology fall within the scope of the EU Waste Electrical and Electronic Equipment (WEEE) recycling directive; how do we dispose of them and who has the responsibility to do this? Typically people throw batteries in the bin rather than taking them to a specific disposal area at say, the local supermarket. How do we change this behaviour?

Of course, pharmaceutical companies have a much bigger environmental responsibility for medical devices, particularly if batteries are included, so they need to consider how best to dispose of them. For example, could patients drop off used devices at the pharmacist,

when they pick up their new prescription? But what happens when patients or carers forget to do this because they are too busy with other things? Should there be some sort of secure envelope that the devices need to be sealed up in, and could this be securely posted or even collected by a pharmaceutical representative? We certainly don't want to increase the burden for the user or their carer.

CONCLUSION

Primarily, for a connected device to be successful, it needs to have features that keep the patient engaged in using it correctly and at the right frequency. It needs to be able to help address the challenge of patient compliance often seen with the current passive devices. In summary, it should be:

- Easy (ideally engaging) to use – promoting right time, right technique
- Low maintenance – minimal setup; easy to dispose or recharge
- Highly portable and easy to find.

If a device achieves the above, it should make a positive contribution to usage statistics. And subsequently, additional connectivity features can be considered, such as delivery history, security and tracking technology, to further contribute to the overall goal of right drug, right time, right amount.

ABOUT THE COMPANY

Bespak, a Consort Medical company, is a full-service drug delivery partner, specialising in innovative patient-centric medical devices. With over 50 years' experience in drug delivery Bespak seeks to apply its proven know-how and technologies to address the ever-changing needs of the pharmaceutical industry, across multiple applications. Bespak partners with customers to design and develop drug delivery devices, as well as providing contract device manufacturing from pilot to commercial scale. As part of the Consort Medical Group, Bespak works with its Aesica colleagues to offer customers an accelerated route to market through a streamlined service, at any stage of the development cycle. As a group, Bespak currently has 10 facilities across Europe supported by a global sales presence including North and South America, China, India and Japan.

REFERENCES

1. *World Health Organisation, "Asthma and COPD fact sheets". (www.who.int/respiratory/en/ Accessed March 2018)*
2. *Lavorini F et al, "Effect of incorrect use of dry powder inhalers on management of patients with asthma and COPD". Resp Med, 2008, 102(4), pp 593–604.*
3. *Restrepo C et al, "Medication adherence issues in patients treated for COPD". Int J Chron Obstruct Pulmon Dis, 2008, 3(3), pp 371–384.*
4. *Global Asthma Network, "Global Asthma Report 2014". (www.globalasthmareport.org/index.php Accessed March 2018)*

ABOUT THE AUTHORS

Collette Johnson works for Bespak in strategic relationship and alliance management, driving successful customer partnerships across multi-functional disciplines to maximise commercial success. Previous to working at Bespak, Ms Johnson worked at Plextek, leading the company's medical business and corporate marketing. She also worked at NHS Innovations with a lead role in bringing together industry and clinical organisations for product adoption and was the programme lead for the national SBRI healthcare programme. While in this role she focussed on the connected healthcare sector and developed a network bringing together industry, clinical and academic stakeholders. Her experience also includes a strategic role in healthcare at Cambridge Consultants for world-leading corporate organisations and innovative start-ups.

Mark Knowles works for Bespak as the Head of Product Engineering, furthering technology and product offerings to support Bespak's respiratory, drug delivery and *in vitro* diagnostic device portfolio. Mr Knowles has over 30 years' experience in R&D, the last 20 years in medical device development. Previous to working at Bespak he worked at Cambridge Consultants (medtech diagnostics) and Elekta Ltd (invasive radiotherapy). Mr Knowles has a great deal of experience translating customer needs into technology solutions, designed for high-volume manufacturing in highly regulated environments. He has an MBA in technology management.