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OFF-THE-SHELF OR CUSTOM-MADE? CHOOSING A DRY POWDER INHALER

In this article, Philippe Rogueda, PhD, Chief Business Officer, Quality Director, Merxin, discusses the manifold factors that need to be taken into account when choosing a dry powder inhaler – beyond just the target disease, formulation and patient population.

Due to the vast number of variables that come into play, development of dry powder inhalers (DPIs) presents a complex challenge. As a result, developers of DPIs face many high-stakes, difficult decisions. One of the most consequential decisions involves the basic approach to selection of the delivery device – will you develop a novel inhaler tailored precisely to your specific formulation and patient population or will you select an off-the-shelf device that you can adapt for your product?

Developing a new device from scratch is costly and time consuming – and comes with all the risks associated with any new technology. In addition to the time necessary for the basic design of the inhaler, a proprietary device will likely require proprietary manufacturing equipment as well as substantial resources invested in regulatory approval. And no matter how much you invest in testing, you will take the product to market with no guarantee that the device will be accepted by clinicians and patients.

On the other hand, for a novel product, customising a device offers certainty that the formulation will have its optimum shot at succeeding in clinical trials and will equally ensure that competitors will have a difficult time producing a generic. For generic products, designing a new non-AB rated device means you don't need to wait for the existing reference product intellectual property (IP) to expire – allowing you

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to launch the generic product earlier. However, marketing non-substitutable generics is more costly than substitutable products, partly due to the need for a sales force. In addition, the non-substitutable inhaler may have trouble competing with AB-rated generics.

Using an off-the-shelf DPI has the potential to get you to market cheaper and faster than developing a new device whilst minimising the risk associated with the delivery technology. However, you lose out on the possible value of the IP, and many developers fear that an off-the-shelf inhaler cannot be fully optimised for their formulation, leading to sub-standard delivery and possible clinical or commercial failure. Is that fear justified? Not necessarily.

A HIGH RESISTANCE DEVICE IS JUST AS GOOD AS A LOW RESISTANCE ONE

Many developers believe that DPI device selection consists entirely of identifying



Dr Philippe Rogueda
Chief Business Officer,
Quality Director
T: +44 1553 403 070
E: philippe@merxin.com

Merxin Ltd
1 Innovation Drive
King's Lynn
Norfolk
PE30 5BY
United Kingdom

www.merxin.com

“The market shows no evidence of a correlation between the delivery parameters of various DPI devices and how well they sell.”

the target diseases and patient population followed by developing a device to do the best possible job of delivering the formulation once the dose and dosing regimen have been established. The 2018 US FDA draft guidance on metered dose inhaler (MDI) and DPI quality considerations specifies that: “Development of an MDI or DPI product should involve consideration of aspects such as aerosol delivery characteristics, portability, ease of use, device constituent part robustness, inclusion of a dose counter, appropriateness of a lockout, cleaning needs and suitability to the patient population.”¹

If it were true that the optimal dry powder delivery device for the formulation is necessarily the best device for the product, then developing a new inhaler for each formulation would be the only way to get the best device. And what do developers believe makes the best device? Much of the industry believes that high-resistance inhalers are better than low resistance; active devices are better than passive; bigger payloads are better than smaller; and simpler design is better than intricate.

Recent research, however, suggests that none of that is true. A 2014 article in *Advanced Drug Delivery Reviews* observes that: “Several misconceptions about optimal inhaler performance manage to survive in modern literature. It is, for example, still widely believed that a flow-rate-independent fine particle fraction (FPF) contributes to an inhalation performance-independent therapy,

that dry powder inhalers perform best at 4 kPa (or 60 L/min) and that a high resistance device cannot be operated correctly by patients with reduced lung function.”²

The authors add: “In practice, excellent results can be obtained with high and medium–high resistance DPIs.” And they note that: “A major advantage of high resistance DPIs is that they reduce the flow rate and this favours central and peripheral lung deposition.”² In fact, studies have shown that, even in the midst of exacerbations, patients with reduced lung function can produce sufficient pressure drop to use high resistance inhalers properly.³ A deep breath might be uncomfortable but it is effective.

The market shows no evidence of a correlation between the delivery parameters of various DPI devices and how well they sell. HandiHaler (Boehringer Ingelheim (BI)), one of the highest resistance inhalers, has demonstrated its ability to deliver medication effectively even for COPD patients with moderately to severely limited airflow⁴ and is also one of the top-selling COPD therapies worldwide. In addition, HandiHaler generates an FPF that is actually higher than the FPF produced by the low resistance Diskus device (GSK), and both of those DPIs sell better than the Spiromax (Teva), which can generate a much higher FPF.

When it comes to active versus passive delivery, Jeff Weers and Andy Clark (both of Respira Therapeutics) have studied that issue carefully and assert that: “Contrary to current industry perceptions, passive DPIs provide the greatest opportunity to

achieve drug delivery to the lungs that is independent of how a patient inhales through a portable inhaler.”⁵

SIMPLE DESIGN IS DIFFERENT FROM SIMPLE USE

As to the idea that simpler devices are better than more complicated ones, it’s true that fewer operational steps leave less room for patient error in using the device – but that is unrelated to the complexity of the device design. Whilst patients may say they feel more comfortable with a simpler device, a simple design will not fix common patient errors such as forgetting to exhale or exhaling into the device. And while it’s true that a simpler design means fewer parts and therefore less cost, a simple design is also simple for competitors to copy.

It is important to avoid confusing complexity of design with complexity of handling. HandiHaler, which is made of 16 parts, requires 11 steps to operate; Diskus is made of 15 parts and requires three steps to operate; Respimat (BI) has 34 parts and requires five steps to operate; and Ellipta (GSK) is composed of 30 parts and requires three steps to operate. Which of those is simple?

What is important is to consider all the factors that may contribute to the success or failure of the product when deciding whether to make a novel device or to adapt an existing device. Those factors go well beyond delivery parameters. In practice, whilst delivery effectiveness is important,

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BOX 1: PERFORMANCE WILL BE JUST ONE OF NUMEROUS FACTORS INFLUENCING YOUR CHOICE OF DPI DEVICE.

- Device performance
- Therapeutic target
- API Dose
- Patient population
- Device aesthetics
- Technology availability
- IP protection
- Investment required and device price
- Marketing preferences
- Financial position of the company
- Regulatory strategy
- Clinical needs
- Technology available at the company already
- Company bias: e.g. Who has the final say? What has been done before?
- Project timelines
- Final aim of the project: e.g. proof of concept for an API, generic product; fully proprietary finished dosage form.

companies usually end up selecting a DPI based on equally important factors such as availability, marketing, company culture, IP, financial or manufacturing requirements (see Box 1). Even for generic products, the choice between fully substitutable or not, hybrid solution or improved device, is more of a strategic and commercial decision than a scientific one.

A GENERIC EXAMPLE: ELLIPTA DPI

Take GSK's Trelegy Ellipta, for example. It's unlikely that anyone optimising a DPI design for a triple combination therapy would come up with the Ellipta device. But the Ellipta inhaler delivers the formulation well enough, reinforces brand continuity, is activated in three steps, offers GSK substantial IP protection, and requires a sizeable investment to copy – making it difficult for generics manufacturers to produce. As a result, potential competitors must choose between waiting years for patents to expire in order to make a fully substitutable AB-rated generic device or adapting a non-substitutable delivery device to the fluticasone/umeclidinium/vilanterol formulation to get to market earlier.

Developers faced the same dilemma with Advair Diskus. Early on – at a time when no off-the-shelf AB-substitutable devices for Diskus, such as Merxin's MRX001, were available – some companies attempted to develop their own substitutable devices but few of those programmes went smoothly. In Europe, Celon's Salmex DPI, which is currently marketed in Poland, was for a while the only fully substitutable approved version of Diskus, after Sandoz's Forspiro.

In the US, where the last Diskus device patent expired in 2016, Sandoz abandoned its generic Advair Diskus programme in January 2020 and, as of March 2020, Hikma was still trying for approval of its version (based on Vectura technology), having resubmitted its abbreviated new drug application (ANDA) in November 2019.

The only US approvals resulted from approaches that at first glance seem riskier. Mylan's Wixela Inhub, approved by the FDA in January 2019, is actually a hybrid in which the user handling experience is the same as the reference device but the dispensing and aerosolisation mechanisms differ. In effect, the development of a hybrid like Wixela resulted in costs and risks comparable to a new device but with the benefits of a generic device. Note that

Wixela was approved as substitutable even though its shape and user steps are significantly different from Diskus.

Taking an even more creative approach, Teva submitted a new drug application (NDA) for a fluticasone propionate/salmeterol DPI using its own Respiclick device and then developed a substitutable generic of its own product – AirDuo Respiclick – instead of Advair. Teva's approach, using a completely novel device, eliminated the need to design around the existing IP and allowed for an earlier launch of the generic product.

Does this mean that developers who want to make generic Ellipta products have to take huge risks?

By far the safest and least expensive path is to wait for the GSK patents to expire and

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make a DPI using the Ellipta mechanism, with a different case if necessary. GSK's Arnuity formulation is protected until 2021, Breo/Relvar until 2025 and Incruse until 2027. The last patents for the Ellipta device expire in 2030 – the same year as the protection for Trelegy and Anoro.

GENERIC OR CUSTOMISED?

The Ellipta device is even more challenging for generic device developers to copy than Diskus, in part because the dual-cavity Ellipta – which is essentially two mini-Diskus mechanisms in a single housing – contains 28 parts, and manufacturing the Ellipta device is known to involve more than 100 suppliers. In addition, the use of dual blister strips in a DPI is protected by a patent until 2028, and other aspects of the design related to the open-inhale-close (OIC) dosing process are protected until 2030. Other companies already at work on substitutable devices for Ellipta have protected their own IP. Designing around existing patents is possible but challenging.

Designing a new device, substitutable or not, to avoid existing Ellipta IP could result in an early filing and would offer

Generic	Customised
Pros	
Substitutable	Own identity
Established technology	High IP protection
Faster to bring to market	Deterrent to generics
Less risk with developing technology	Performance tailoring
Able to use established supply chain	Adaptable to API/formulation needs
Familiar with patients and doctors/nurses	Improved patient handling
Known performance	Opportunities to simplify manufacturing
No need for extensive sales force (generics case)	Opportunities to benefits from latest device technology
Cons	
No control of identity	Will require extensive demonstration of usability
Limited IP protection	New tools will be needed
Others will copy your device	New technology might bring up unexpected development challenges
Device performance is fixed, only formulation can change	Unknown risks associated with new technology

Table 1: Summary pros and cons of generic and customised devices.

IP protection and the potential for added benefits such as improved functionality. A new device with better aerosolisation might allow for a lower dose to achieve a similar clinical effect – or the new inhaler might provide a better user experience with fewer handling errors and could possibly help a generic product to command a higher price than a 505(j) option. This route, however, involves more risk and cost (Table 1).

The hybrid option of keeping the user handling experience while modifying the dispensing and aerosolisation mechanisms, although somewhat more expensive and riskier than copying the originator device after patent expiry, ensures an AB-rated device and can open the door to an early filing before expiry of the originator patents. Merxin's MRX006 dual cavity DPI, for example, is designed specifically to enable a generic 505j dual or triple combination therapy product to be filed before existing patents expire.

WHERE TO TURN FOR HELP

Whatever route you choose, it's important to finalise device selection as early in the

development process as possible because using a placeholder device early on has the potential to result in catastrophic delays if regulatory agencies require you to repeat clinical trials with the device that will be marketed.

That's why it is critical to consult companies like Merxin that have expertise in regulatory and market issues, as well as proven success in the engineering and design of DPIs. We will help you to define realistic boundaries for your decision, taking all important factors into account, to reduce risk and cost no matter what you decide.

Our track record with generic HandiHaler and Respimat is a testimony to our expertise and ability to deliver inhalers. Our expertise supports your projects.

ABOUT THE COMPANY

Merxin designs and supplies generic and customised inhaler device platforms, including multidose dry powder inhalers, capsule dry powder inhalers, soft mist inhalers, no heat no PG vaping devices and devices tailored to cannabinoid delivery to the lungs and nasal cavities. Customers

combine Merxin device platforms with their drug formulation to make final dosage forms that are supplied to users and patients. Merxin has been assessed and certified as meeting the requirements of ISO 13485:2016 for the Design, Development and Supply of inhalers. Established in the UK in 2015, with manufacturing capacity across the globe and an international client base, the company is adding more products to its portfolio and expanding rapidly.

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ABOUT THE AUTHOR

Philippe Rogueda, PhD, FRSC, CChem, CSci, CIng, EURIng, Co-founder and Chief Business Officer of Merxin, is a Fellow of the Royal Society of Chemistry and OINDP expert with an accomplished track record delivering technology and global projects across R&D and commercial industrialisation. Dr Rogueda has held a number of positions in the inhaled drug delivery space, starting as a formulation scientist in the pMDI formulation labs of AstraZeneca; as a principal scientist at Novartis designing DPI, nasal and nebulised inhaled therapies; as an Executive Director of Inhaled Products R&D at Actavis/TEVA; before setting up Merxin to make inhaler technology accessible to a wider audience. Rogueda is principal consultant at Aedestra (Hong Kong), founder of Inhalation Asia (Hong Kong), and of Anthocan (UK) a company dedicated to the formulating of inhaled cannabis therapies.



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GENERIC & CUSTOMISED

MRX006 is a multicavity multidose dry powder inhaler (DPI). MRX006 is based on the open-inhale-close principle. It is suitable as an AB-rated substitutable device for triple therapy combinations: vilanterol, umeclidinium, fluticasone.

