# LEARNING TO WALK BEFORE WE RUN: BASIC PROBLEMS WITH INHALERS PERSIST, & WHY IT IS WORTH SOLVING THEM

By David Harris

The humble pressurised metered dose inhaler (pMDI) is celebrating its 60th birthday this year and it has certainly stood the test of time. Not a lot has changed since it was introduced all those years ago. In the region of 680 million pMDIs are used annually[1] to treat people suffering with asthma or COPD (chronic obstructive pulmonary disease), which equates to approximately 2,500 shots fired around the world every second. These numbers are astonishing and, unfortunately, numbers that are on the increase as incidence of respiratory diseases continue to rise.

The pMDI is tremendously popular – the first choice of medication in many countries – yet 90% of asthmatics and COPD patients cannot use them correctly.[2] This shouldn't really come as a surprise though – let's face it, there are a number of well-known challenges pMDIs present to patients…

The first challenge is that patients are instructed to "breathe in deeply and slowly".

There is a substantial body of research that shows just how beneficial inhaling at a low flowrate is, in terms of increasing deep-lung deposition, reducing mouth and throat deposition, and achieving consistency in the delivered dose. Yet pMDIs are very easy to inhale through – they offer practically zero resistance to the airflow, meaning that patients are often able to inhale at ten times the optimal flowrate. And why wouldn't they? After all, it's in their best interest to get the event over with as quickly as possible, right? Wrong, actually. And what flowrate constitutes "slowly" anyway? It's very subjective. Yet the benefits of inhaling below 40 L/min are clear and demonstrated[3] – lung deposition can be as high as 50% – compared with just 8-12% for those who choose to inhale as quickly as possible.

Compounding this already significant issue, is the fact that standard pMDIs require the user to co-ordinate the pressing of the canister correctly with their inspiratory manoeuvre. This is a difficult task to achieve, and continues to thwart many experienced asthmatics, even those with the best intentions. Over the six decades that the pMDI has been in existence, only two automatically (breath)-actuated products have ever made it to market – 3M's Autohaler and IVAX's (now Teva's) Easi-Breathe.

There are several breath-actuated pMDIs currently undergoing development but engineering a suitably robust and scalable mechanism is particularly challenging, due to the huge difference between the force required to press the canister (typically 25-30 N) and the tiny force that can be created by someone inhaling (typically a small fraction of one Newton). This difference – which is several orders of magnitude –

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**David Harris**
Respiratory Drug Delivery Specialist
T: +44 1763 267 608
E: david.harris@paconsulting.com

**PA Consulting Group**
Cambridge Technology Centre
Melbourn
Herts
SG8 6DP
United Kingdom

**www.paconsulting.com**

means that designing a mechanism that fires correctly when a patient inhales but doesn't fire when you accidentally drop the primed inhaler, for example, is exceedingly difficult. Unfortunately, clever, automatic inhalers such as these end up costing much more to produce, and consequently are only prescribed to patients who are deemed to have significant issues with standard pMDIs.

So given that asthma and COPD are both on the increase, together with the direct and indirect costs of non-adherence, then surely there must be a vast amount of research and development activity seeking to address these two major issues with the pMDI? I'm afraid not. There is, however, substantial time and effort being devoted to developing "smart" inhaler technology that, for example, enables inhalers to connect to smartphones and provide information such as when and where the patient took their medication.

The potential here is staggering. The metadata will have extremely high long-term value as analysis could reveal currently unknown correlations (for example, the effect of particulate concentrations on frequency of reliever use) and eventually may even pre-empt the likelihood of exacerbations. However, this recent upsurge in adding intelligent electronics to sixty year old technology raises a number of questions.

- Who owns the data?
- How is it stored and managed securely?
- Who's going to mine it for useful information?
- Who will pay the additional cost for the intelligent part of the device?
- How will the provider be recompensed?
- What patient benefit will it actually deliver?

So, whilst the potential of adding connectivity is considerable and should not be ignored, the unknowns are too, begging the question: is this really the priority? Why not fix the basic and well characterised pMDI use issues first, then add connectivity and varying levels of intelligence if it adds further value or benefit and is commercially viable?

The honest answer is that it is actually probably easier to add connectivity to pMDIs than to find solutions to their fundamental issues. Inhalers, and the science that underpins how they work, are highly complex and not very well understood. Take dry powder inhalers (DPIs) for example. You have multi-phase fluid dynamics, bulk powders – often comprising a blend of three polydisperse size fractions, electrostatics, cohesive and adhesive forces – compounded by moisture-dependent capillary interaction, not to mention the vast number of influencing variables at play. It's difficult! I've heard people refer to it as "rocket science" but actually, in many ways, it's probably harder, for we can design and build very efficient rockets and, relative to inhalers, the science behind rockets is reasonably well understood.

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But inhalers need to be improved for a great number of reasons. For example, considerable resources in the inhalation devices industry are currently being focused on copying successful, off patent products in order to produce cheaper alternatives. Whilst this is an honourable and ethical thing to do, as a collective body of individuals working in this sector, it should be forefront in our minds that there are still fundamental issues with the original delivery technology that need to be solved rather than copied. Not least because pharma companies working on new chemical entities (NCEs) frequently struggle to find suitable inhaler devices to enter clinical studies with confidence, and thus often resort to conducting early studies with a nebuliser, knowing that this will not be their eventual preferred route to market.

A cursory look through any of the recent parenteral drug delivery-focused issues of ONdrugDelivery Magazine reveals how the widespread availability of true device platforms for parenteral delivery is transforming the sector, rapidly advancing and accelerating the development of products suitable for self-injection. In contrast, platform technologies in the DPI space simply don't exist, at least beyond generic, off-patent capsule inhalers. Each drug formulation and device combination is carefully tailored to meet the required regulatory standards, and this process takes a long time to achieve a robust quality product.

It typically takes between eight and ten years to develop a generic DPI product.[4] If better-performing DPIs existed, as true platform offerings, developed using more modern science, engineering and analytical techniques, pharma companies would potentially have lower-risk route to market available to them. Higher performance, in terms of higher fine particle fraction, mathematically leaves less scope for variability and consequently will deliver better dose content uniformity. So it's a win-win; pharma companies achieve more consistency in their clinical data, and patients receive more drug where it's needed and less in the mouth and throat.

So why are there not more people working on developing innovative inhaler technologies? There are a number of reasons…

Firstly, it's a very cost-sensitive market and DPI device and development costs are higher than pMDIs. Secondly, globally, there is increasing pressure to reduce the cost of healthcare – and conditions that are

on the rise, such as asthma and COPD, combined with increasing populations – only exacerbate this situation. It's much easier not to "rock the boat" – copying successful generic products to offer lower cost products is in many ways a sensible thing to do despite the problems in the usability of pMDIs.

However, looking at the cost of non adherence and suboptimal use more closely suggests that pursuing the generic route is merely a short term solution. The resultant costs of non adherence are significantly higher than the cost of treating the condition properly in the first place. Physician visits and hospitalisations alone cost more than the global market value of inhaled products.[5] Furthermore, these are only the first-order costs and factoring in second-order costs such as time off work it soon becomes very clear that addressing the fundamental issues can lead to substantial cost savings on a global scale. The questions then become: who benefits from these savings, and how will the companies who have found technical solutions be recompensed for their effort and insight?

There are additional advantages, beyond saving money, that result from driving inhaler technology forward. Many systemic drugs require higher payloads and tighter control of the delivered fine particle dose than current inhaler technology permits. Some of the notable products that have made it to market, such as Mannkind's inhalable insulin, Afrezza, have relied on novel particle engineering in order to achieve regulatory approval – device technology alone wasn't sufficient. Perhaps if suitable aerosolisation platforms existed, the time to market for such products could be reduced, and research for the pulmonary delivery of drugs for therapies beyond asthma and COPD would be a more attractive proposition.

The rate of advancement of computers, tablets and smartphones, combined with progressive manufacturing technologies and new and novel materials, is in some ways overwhelming for pharma companies. Inhaler device technology is seriously lagging, with only connected and smart devices showing any real innovation or promise within the sector. Whilst there is a lot of ongoing research aiming to improve formulations, devices, and increase understanding, it takes many years for laboratory-scale research to translate into commercial products that benefit the patient.

What's required is firstly recognition and then acceptance that fundamental issues with inhaler products persist. We need a concerted effort to improve these basic shortcomings, and a focus on building future platform technologies that will benefit the patient and provide pharma companies with a more efficient route to take NCEs to market. Valuable lab-based research projects need to be identified, prioritised, and adequately funded in order to reduce the long timescales and relatively low likelihood of success. Only then will the escalating costs resulting from non adherence and sub optimal inhaler use be truly within our control.

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## ABOUT THE AUTHOR


**David Harris** leads the Respiratory Drug Delivery sector at PA Consulting and enjoys the challenge of balancing commercial and technical activities, saying: "One of the best things about working at PA is being surrounded by like-minded and intelligent people – many of whom are leaders in their field. Drug delivery is a hugely exciting sector to work in and it offers a wide range of technical and scientific challenges. It's also very rewarding – the products that we and others like us develop have the potential to massively improve people's lives. It's a great pleasure working with clients who share these aspirations."

Mr Harris is a physicist and has been working in the field of medical device development since 1994, where he started his career in the Respiratory Physics group at Fisons. He specialises in respiratory drug delivery and enjoys applying solid aerosol science and fluid dynamics to improve the efficacy of inhaler technology. David has numerous patents and publications in this area and regularly presents at conferences.