

Respiratory Drug Delivery – What has Happened and What might the Future Hold?

Recent decades have seen vast technological developments the world over. Here we look back at some of the recent defining moments for the respiratory drug delivery sector and take a look forward at the areas that are set to define the industry in years to come.

In the era of Pac-Man, big hair and Whitney Houston, a defining moment for respiratory science was the signing of The Montreal Protocol by 167 countries in 1987. Introduced to protect the ozone layer by phasing out harmful substances, this international treaty forced a pivot in the type of gases used in millions of asthma inhalers. The chlorofluorocarbon (CFC) propellants widely used in pressurised inhalers at the time were phased out and replaced by newly-developed hydro-fluorocarbon- (HFA-) based propellants. The effect of the move away from CFCs also kickstarted investment by pharma companies into alternative propellant-free drug-delivery methods, like dry power inhalers which have now become commonplace alongside more traditional press-and-breath inhalers.

Respiratory drug delivery has equally been defined by the development and approval of new drugs and treatments. 1990 saw the launch by Glaxo (now GSK) of Salmeterol, one of the most widely-used medications for asthma and COPD management today. Salmeterol was the very first long-acting beta-agonist (LABA), to be taken regularly to control chronic symptoms and prevent asthma attacks. This was followed by Seritide/Advair in 1998 – a combination of salmeterol and fluticasone propionate – which remains the best-selling asthma treatment of all time, generating annual revenues of over \$7 billion.

Another ground-breaking drug introduced in recent decades is TOBI (tobramycin solution for inhalation); approved by the FDA for the treatment of cystic fibrosis (CF) in 1997. It was the very first inhaled antibiotic for the treatment of CF and has been credited with significantly extending the life expectancy of CF patients. Uniquely,

this drug was deemed to be so important to health that it was developed by PathoGenesis Corporation in collaboration with the academic inventors, the National Institutes of Health, the U.S. Food and Drug Administration, and the CF Foundation.

While there is a lot to be learnt from successful products, there is perhaps more to be learnt from failed ones. My final key milestone is Pfizer's Exubera; the first ever inhaled insulin drug/device combination to be approved by the US FDA in 2006. At the time, the use of the pulmonary pathway was considered a major breakthrough in diabetic treatment. However, for Pfizer it ultimately ended in disappointment when they withdrew the therapy after less than two years. Part of the therapy's shortcoming for patients was the inconvenient size and complexity of the delivery device. Pfizer wrongly believed that the inadequacies of the device would be outweighed by the benefit of not needing to self-inject insulin, but this didn't play out as they had expected. Most diabetics ultimately favoured a small and discreet injection to a cumbersome inhalation device.

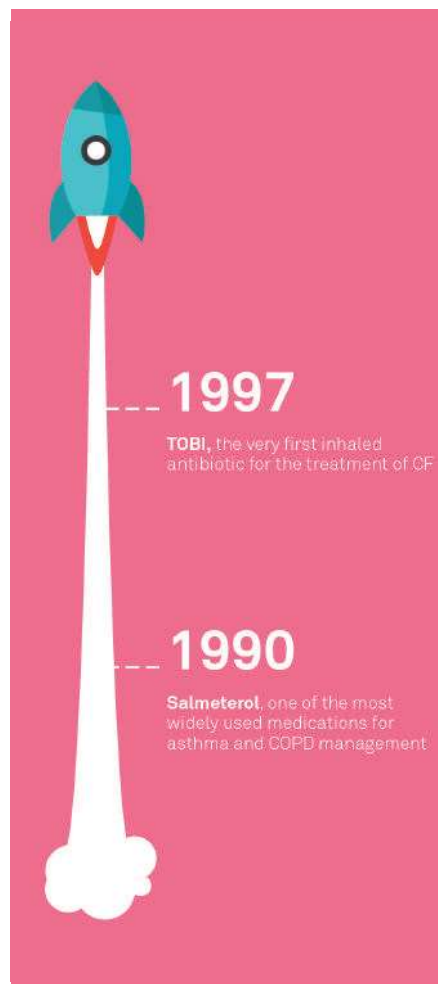
For device developers, Exubera remains one of the most interesting examples in recent history of how a poor understanding of patients' needs resulted in a difficult-to-use delivery device which contributed to a major failure to gain market acceptance, at the estimated loss of \$2.8 billion to Pfizer.

But what about 2020 and beyond?

Looking ahead, for me there are three key areas which will define the future of respiratory drug delivery. The first is adherence, and efforts to improve patient compliance with therapies. Secondly, I think we will see much greater focus on prevention and management of diseases like asthma and COPD, as preferable to intense treatments. And last is the topic of sustainability; the environmental impact of this industry and our responsibility to limit it. But how and why will these three things impact drug delivery?

Patient Adherence

The challenge of improving patient adherence remains a major theme for the



delivery of inhaled medicines. Worldwide, non-compliance is a major challenge to the delivery of healthcare. This is because consistent patient adherence to medication and treatment therapies is both crucial to successful disease management, and extremely difficult to ensure.

In 2003, the WHO estimated that only 50% of patients successfully take their medication as prescribed; non-adherence is not only detrimental to patient health, but also has vast cost implications for healthcare providers. Adherence is also directly linked to sustainability because the better patients follow their medical instructions, the less wastage and overuse of medicines and devices there are.

Julian Dixon, Director of Human Factors at Team Consulting, tries to explain the difficulties.

"We humans often don't do what we know we should. Perhaps it is one of the things that makes us human. Unfortunately, many medicines still depend on us as part of their delivery system, and most of us aren't that dependable when it comes to adherence with our medication. Non-adherence is an elephant of a problem: it is in every room where pharmaceuticals are talked about and it will be tackled one step at a time. We can attempt to tackle the non-adherence elephant by reducing the burden on users, by making administration less unpleasant, by eliminating ways of going wrong and by providing memory aids and reminders."

"Those measures make it easier to adhere – e.g. fewer, easier administrations – but don't address the non-adherence 'hard problem', which is that it is rooted in our human capacity to not do what is in our interests. Adherence with medication is one human challenge amongst many hard-nuts-to-crack: smoking cessation; adequate exercise; healthy diet."

Thanks to the importance of 'good adherence' to patient health and recovery, there are significant efforts across the industry to make improvements. Recently, there have been attempts to tackle non-adherence through new technologies, such as companion apps that give patients reminders to take their drugs and device training instructions. These apps may be specific to a certain therapy or device, but there are now also many versatile 'virtual pillbox' apps – such as Medisafe and Dosecast – which can log patients' doses and symptoms for any condition. These apps send push notifications to remind patients to take their medication, and will even notify a friend or family member if the patient forgets.

These companion mobile apps can also work alongside increasingly common 'smart' devices that actively assist a patient to inhale correctly, to improve the drug delivery effectiveness. One example is Teva's ProAir Digihaler, which is the first FDA-approved connected inhaler. However, new technology also has a downside; it increases the device cost and complexity, so the technology gains need to be carefully weighed and balanced against the therapy's benefits.

Greater Focus on Prevention

'Prevention is better than cure'. It is neither a new or novel concept, but nor is it one that has been well championed in the respiratory



health space. In recent years, we've finally seen a shift in perspective to see diseases like COPD and asthma as intrinsically linked to our environment, lifestyle and overall health.

Using technology to make more regular check-ups accessible will help respiratory health problems to be identified early, or even pre-empted. Nowadays there are more devices and technologies than ever to encourage people to stay healthy. In the consumer world, sensor technologies are being increasingly utilised to track heart rate and pulse, body temperature, glucose and blood oxygen levels. Devices such as FitBit and Apple Watches record activity and fitness levels and accompanying smartphone apps help users track their fitness, and act as motivation.

Using technology in the respiratory health sector for preventative measures is less common but not unheard of. Recently, GSK have partnered with the Weather Channel, utilising data on upcoming weather events to improve effectiveness of respiratory care solutions. There also now exist smartphone apps available to help measure and monitor lung health and function, such as the Aria: Spirometry and Lung Health app.

These types of innovative solutions provide individuals and healthcare providers with more information about individuals' health – important information that can improve diagnosis and treatment, keeping them healthier longer, allowing them more control of their respiratory health.

Sustainability

There is increasing demand for more sustainable product design in the medical device industry. Whilst sustainability has been on the agenda for several years, the medical industry moves slower than our consumer counterparts, many of whom have already made serious changes to reduce the environmental impact of products and packaging.

There remains the complex underlying issue of finding a balance between 'patient health' and 'environmental health', especially when each affects the other. Typically, major shifts in the medical devices industry only come about when pushed by regulation; there will certainly need to be adaptations in the respiratory industry to reduce our environmental impact and we should expect some developments in this area soon. We think that it can be tackled right now in several key ways:

1. By working on manufacturing processes to reduce production waste and reduce the need to ship materials, components and sub-assemblies to different manufacturing sites.
2. By specifying materials with a reduced carbon footprint during the development of new devices.
3. By reducing the amount of device packaging that is delivered to the patient; for example, by combining packaging and instructions for use or by using simple cardboard support trays.
4. By setting up and supporting programmes that deal with the collection and recycling of used devices.

The environmental impact of modern inhaler devices is the key area of debate when it comes to sustainability in the industry. The vast majority of the 10 million asthma patients in Europe use pressurised metered dose inhalers (pMDI). These plastic devices, produced in mass, release propellants which are damaging to the atmosphere. They are also not reusable and are very difficult to recycle; most are incinerated, releasing more harmful gases.

At the beginning of this article I mentioned the impact that the Montreal Protocol has had on inhaler devices; by phasing out CFC gases and triggering the development and use of HFA-based propellants. However, HFAs, while not as damaging to the ozone layer – with a carbon footprint one-eighth the size of that of CFCs – still represent a potent greenhouse gas, and calls for discontinuing or at least limiting their use are growing. The problem with this is that, whilst current propellant-based inhalers may be detrimental to the environment, they are also an important part of the lives of millions of patients worldwide. This raises a big question; should we potentially sacrifice patients' disease management by withdrawing or changing devices that are environmentally damaging? Or, should patient health take priority over environmental protection?

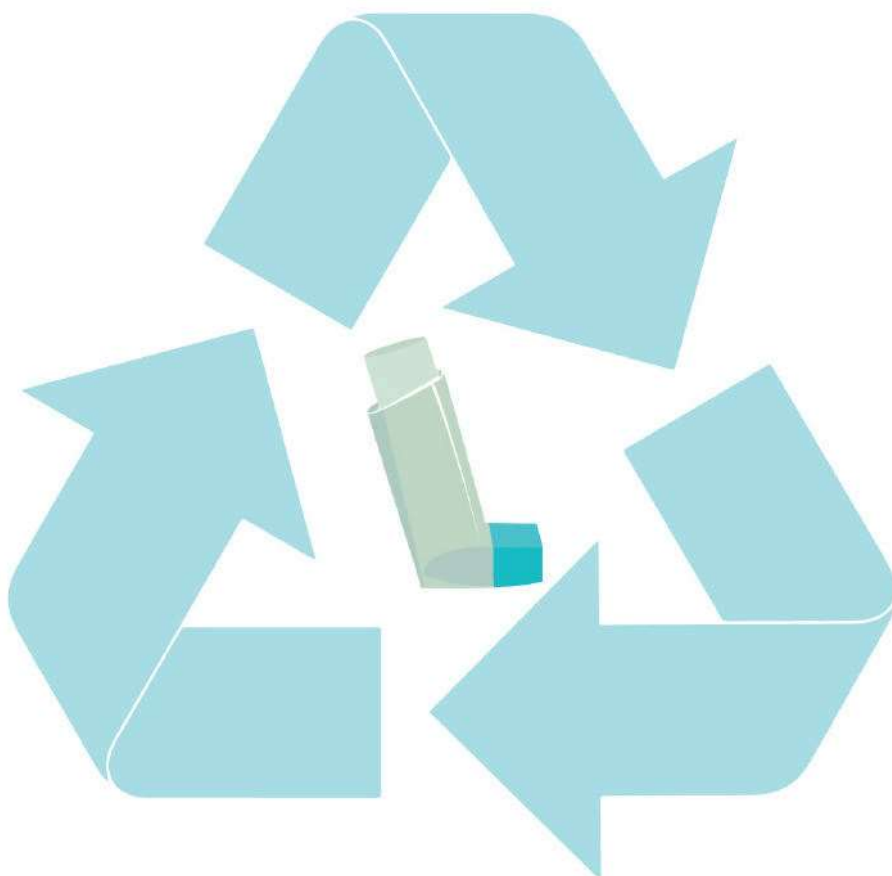
There is no easy answer, but significant effort is being spent to find a reasonable solution, including the development and approval of more environmentally-friendly HFA propellants and other inhalation technologies with reusable elements.

Speaking of other inhalation technologies, the second key impact of the



Montreal Protocol for the respiratory industry was the growth in research effort into other device-reliant drug-delivery methods such as dry powder inhalers (DPIs). DPIs work without propellants, instead using patients' respiratory effort to aerosolise the drug, and their carbon footprint is less than a tenth of that of pMDIs. Because of this, government and healthcare bodies continue to encourage the shift away from pMDIs towards dry powder alternatives. However, where the environment is concerned, there are still issues around the overall sustainability of single use devices.

More thought is also being given to how devices are managed at the end of their lives, recovering devices to recycle the materials used (rather than incinerating them as usually happens). Inhaler recycling schemes have been introduced in many areas – Teva recently launched one such scheme in Ireland, and GSK have recycled 1.2 million inhalers since 2010 as part of their 'Complete the Cycle' recycling and recovery scheme. Unfortunately, these schemes only recycle the gas and metal canisters; the plastic elements that make up the bulk of the devices are still being incinerated. There are areas where incineration is used to generate power, but the industry is in need of a more sustainable recycling





solution for such vast numbers of plastic inhalers.

Making products reusable is one such solution which is gaining traction in the market. For example, Boehringer Ingelheim's Respimat® inhaler is now reusable, with patients receiving with each inhaler up to six replaceable cartridges containing their medicine. This alternative approach

drastically cuts down on the amount of plastic used and then disposed of, without having to significantly change the core drug delivery mechanism.

In my career I have worked on various dry powder inhalers, including a concept for a novel inhaler that is essentially a cardboard tube with a simple piercing mechanism to release the drug from an

innovative single-dose blister. This approach is novel not only because it uses advanced blister technology, but also because it vastly reduced the complexity and physical mass of the device; another approach to more eco-friendly product design. It has generated a lot of positive interest; pioneering solutions like this should be seriously considered in the next few years to supplement current respiratory device offerings and encourage more sustainable product design.



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Brennan Miles is an experienced respiratory drug delivery consultant. Prior to joining Team Consulting, Brennan spent several years with the pharmaceutical giant Pfizer. He has been involved with and led the development of a range of respiratory devices, as well as surgical, injector and ophthalmic devices for a wide variety of therapies. He is the named inventor on a number of patents and has also had several papers published. Team Consulting is an award-winning medical device design and development consultancy. For over 30 years we have worked closely with our clients at the world's leading pharmaceutical and device companies to develop better medical devices.