The future of inhaled medications and inhalation technology:

formulations, devices and strategy through non-clinical development

In this article, **Simon Moore**, Director of Inhalation Science and Engineering at Envigo, provides thought leadership into current trends in the development of drugs for treating both respiratory and systemic diseases, drug formulation, and inhalation technology.

Inhalation delivery—not only the domain of respiratory diseases

Historically, inhaled drugs have been used to deliver medicines targeted at the main respiratory diseases, namely asthma and chronic obstructive pulmonary disease (COPD). Current estimates suggest that as many as 235 million people worldwide have asthma and over 200 million people have COPD, with rates set to increase, particularly in China and other developing countries (see Graphic 1).[1] The need for efficacious medications for these incurable diseases is still a major focus for research, and off-patent drugs are able to bring in large revenues. In the US, for example, GSK's Advair® (Seretide) came off patent in 2010 but still generated revenues of >$US 8 billion per annum in 2012 and $US 5.5 billion in 2015.[2]

The combined drugs market for asthma, COPD, cystic fibrosis (CF), and idiopathic pulmonary fibrosis (IPF) alone was $US 28.1 billion in 2015 and is predicted to expand by more than 50% by 2022 (see Graphic 1).[4]

Other respiratory diseases, such as infections, tuberculosis, and lung cancer, are also a large worldwide health burden, and there is no quick or easy solution to meet this future global challenge.

Delivering respiratory medications directly to their site of action in the respiratory system is an obvious advantage of inhalation formulations, but there are other benefits too, and it is these additional benefits (see Graphic 2) that are driving research into inhalation treatments for systemic diseases.

One of the first well-publicized inhalation products for treating a systemic disease was Pfizer's Exubera®. An inhaled form of insulin for treating diabetes, Exubera® was withdrawn in 2008 due to poor sales blamed, in part, on the bulky and inconvenient inhaler. Initially a setback to innovation in this sector, the failure of Exubera® resulted in other companies reconsidering similar product developments. However, in June 2014 the United States Food and Drug Administration (US FDA) approved Mannkind's Afrezza®, an inhaled insulin product.[7] The current market success of this product appears limited, but may relate to the need for specific patient screening and product pricing rather than the efficacy of, or preferences for, the inhaled medication.[8]

Exubera's® withdrawal has certainly not hindered the interest in inhalation delivery, quite the opposite in fact. In the last four years, 1,350 active inhalation studies—for new, combination, and existing products, encompassing 802 different diseases and 105 rare diseases—have been

About the author

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Simon joined Huntingdon Life Sciences in 1999 as an inhalation study analyst, in 2016 he was promoted to his current position with managerial responsibility for the inhalation engineering services and aerosol technologist groups.

In this role, Simon is responsible for all aspects of aerosol technology, including the overall interpretation and reporting of the inhalation studies at the Huntingdon site. The inhalation engineering services groups designs, prototypes, and manufactures custom-made inhalation equipment for all inhalation sites within the Envigo organization.

Simon obtained his degree in Chemistry from the University of Dundee (1996) and gained his PhD from the University of Glasgow (2000). Simon is the Vice Chairman of the Association of Inhalation Toxicologists, a committee member of the British Standard Institution on Nanotechnologies, is involved with the NC3Rs CRACK-IT program, and has produced over 100 publications.

GRAPHIC 1: Respiratory disease facts[1,3–6]

Asthma
235 million
people worldwide
The **most common** chronic disease worldwide

COPD
>200 million
people worldwide
Predicted to be the 3rd leading cause of death worldwide by 2030[3]

Cystic fibrosis (CF)
70,000 people
have a diagnosis of CF worldwide[5]

Idiopathic pulmonary fibrosis (IPF)
3–9 cases
annually per 100,000
in Europe and North America[6]

Respiratory market size for these conditions[4]
$28.1 billion
in 2015
$46.6 billion
in 2022

Sleep disordered breathing
>100 million
people worldwide

Acute respiratory infection
4 million
deaths annually worldwide

Pneumonia
is the **most common** serious respiratory infection, accounting for
>1.3 million
deaths of children under 5 years of age annually

Influenza kills
250,000–500,000
people
and costs
$US 71–167 billion
annually

Tuberculosis
8.7 million people
develop TB annually worldwide

Lung cancer
1.37 million people
die from lung cancer annually
Most common
form of cancer

logged with the US FDA clinical trial register. More than half of these inhalation studies are for systemic conditions.[7]

Inhalation devices and formulations

As previously indicated with the Exubera® inhaled insulin device, the success of inhaled medications depends on two key considerations: drug formulation and the inhaler device itself. Innovations in both these aspects of design are leading to more effective drugs—new, combination, and generic—although improved powder formulations may be developed more cost-effectively than new, sophisticated inhalers.[9]

Inhalation devices

A considerable amount of development time, effort, and money goes into the production of any inhalation device as it can contribute to the drug's success, irrespective of how effective and beneficial the drug may be to the patient. Inhalation delivery offers something that is unique compared to other routes of administration: when used in combination, it provides extended patent protection. In the US, for example, GSK's Advair® (Seretide) came off patent in 2010, although the Diskus delivery device remains in patent through 2016.[10] To be effective, an inhalation device must be matched to the patient, easy to use, forgiving of poor technique, and able to provide feedback to the user about dose emission and technique (Table 1).

The size of the market for respiratory inhaler devices continues to expand, with estimates suggesting it will reach $US 43 billion by the end of 2025—a compound annual growth rate (CAGR) of 4.3%.[12]

Formulations for inhalation

Traditionally, the fine drug particles required for delivery in Dry Powder Inhaler (DPI) devices have been produced by mechanical micronization using air jet mills. These fine particles are then often combined with a lactose carrier to improve drug stability and dose control, depending on the drug type or compound class. More recently, however, particle engineering techniques look poised to transform future drug formulations (see Box 1).[9] These new techniques have the potential to provide a more efficacious drug, allowing lower doses to be used and reducing the potential for side effects.

Nanotechnology

Nanotechnology needs special mention. Clearly the size of the particle is pivotal for inhalation studies in ensuring effective lung deposition. However, nano-sized materials are broadening the options for development. Nanomaterials are defined as particles that have one or more external dimensions 1–100 nm in size.

The market for nanotechnology usage in medicine is huge, with applications in diagnosis, prevention, and treatment.[13] It is predicted that by 2021, the nanotechnology-enabled drug delivery market will be worth $US 136 billion, which would represent 15% of nanomedicines globally.[13] Despite

GRAPHIC 2: Benefits of inhalation delivery[7]

Compared with oral administration:	Compared with parenteral administration:
Avoids degradation in the GI tract and first-pass metabolism	Improved stability, especially for proteins and peptides
Less drug could be required	Painless and less intrusive, which may aid patient compliance
Lower dose levels with potentially fewer side effects	Costs may be lower
Suitable for drugs that are not absorbed orally	Storage and transportation options may be simpler
Onset of action may be more rapid	No risk of localized injection site reactions and infection

BOX 1: Examples of some particle engineering techniques[9]

'Drying' techniques

- Examples include spray drying, freeze drying, and vacuum foam drying

Supercritical fluid technology

- The drug is dissolved in a supercritical fluid; particles form due to rapid expansion of the fluid or by precipitation from the fluid

Superprecision particle molding

- Allows molecules of any size or shape to be molded or 'printed.' Liquidia Technologies proprietary PRINT® platform is one example

Carrier platforms

- Where the drug, or drugs, are combined with a carrier technology that allows the free flow of particles deep into the lungs. Examples include:
  - Pulmatrix's iSPERSE® platform—their PUR1900 drug for fungal infections in the lungs of cystic fibrosis patients is one candidate currently in clinical testing[16]
  - Mannkind's Technosphere® Technology—used in their insulin product AFREZZA®

Sonocrystallization

- Uses an ultrasound-controlled crystallization technique. For example, the Prosonix platform from Circassia Pharmaceuticals plc—its fluticasone propionate pressurized metered-dose inhaler (pMDI) has been approved as the generic equivalent of GlaxoSmithKline's FLIXOTIDE® pMDI by European decentralized procedure, following a filing to the UK Medicines and Healthcare Products Regulatory Agency

TABLE 1: Desired physical characteristics of devices[11]

Primary	Secondary
Easy to use • To avoid additional stress during an acute attack • Simple treatment implies a less 'serious' disease that is under control **Discreet** • The device should not attract attention during administration • Small—it should fit into the palm of the hand • Unobtrusive style without bright colors to avoid appealing to children **Portable** • Should fit easily into a trouser or jacket pocket **Visible dosing** • Remaining doses should be visible to allow the patient to anticipate when a new prescription will be required	**Easy dose loading** • Should be possible to load dose into the device quickly and hygienically **Clean and hygienic** • Should be simple to protect and clean the mouthpiece **Separate device and doses** • To avoid additional costs and wastage

this exciting prospect, there are still public concerns about the safety of nanomaterials, particularly for engineered materials, because the long-term effects of these materials is still unknown.

Inhalation technology strategy through discovery and regulatory non-clinical development

Of the various considerations when planning efficacy and toxicology studies using inhalation technologies, regardless of formulation, dose delivery methodology and the reproducibility of effective dosing are two of the most important.

The main methodologies for drug delivery in non-clinical studies are intratracheal and inhalation dosing. Intratracheal dosing involves anesthesia and intubation, with the drug delivered via bolus through the intubation tube, and is principally used for early screening studies. This method is simple, uses minimal amounts of drug, and the delivered dose is easily quantified. However, it is prone to artefactual toxicological and pharmacological results, and the particle size used in testing often differs from that which will be used non-clinically.

Inhalation dosing, on the other hand, delivers compound to conscious animals by the clinical route of administration—that is, the lung—removing the risk of intratracheal artefacts. The essential aspect of this method is the necessity for specialist inhalation technology capabilities and experience. Having the ability to reproducibly control the aerosol during both intra- and inter-exposures is pivotal in ensuring study integrity is maintained; failure to achieve reproducible control may compromize study endpoints, allowing poorer data interpretation and reducing the scientific impact of the study. At worst, the study may need to be repeated if the aerosol is not controlled effectively.

Having the ability to reproducibly control the aerosol during both intra- and inter- exposures is pivotal in ensuring study integrity is maintained

Envigo has conducted nearly 2,000 inhalation studies in the last nine years and >100 inhalation studies on drugs formulated using new, novel formulation techniques. Our experience with these formulations is that the aerosol concentration is more consistent, reproducible, and aerostable than standard, lactose-based carrier formulations, which improves study conduct, decreases potential animal-to-animal variation, and reduces the overall amount of drug required to conduct the study.

Compound requirements is always a topic for discussion with inhalation studies as it requires larger amounts of drug than other routes of administration do, although a considerable number of practical techniques can be employed to minimize the dose.[14] We have worked collaboratively with a number of clients to develop more efficient methods for inhalation delivery of powders, including developing a capsule-based aerosol generator (CBAG) with GSK that offers significant cost savings over commercially available instruments.[15]

It is also important to consider that the FDA assumes 100% deposition of a delivered dose in humans, 10% in rodents, and 25% in non-rodents.[14] When planning dosing experiments, it is important to take this into account in order to ensure adequate dose coverage.

Conclusions

In seeking competitive advantage, companies are increasingly considering alternative solutions to the historic method of drug discovery. These include route switching of established products to extend the product's value proposition, de-risking drugs earlier in the product-development timescale by incorporating additional endpoints into early *in vivo* studies, and further

innovative reformulations and particle engineering.

Inhalation delivery will continue to be utilized for drugs targeted at both respiratory and systemic diseases, which will continue to grow, even when cures for all of these diseases can be found.

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KEY POINTS

- **The inhalation route of drug delivery is increasingly being explored for medicines that target systemic diseases—it is no longer the preserve of respiratory drugs.**
- **The success of inhaled medications depends on both the inhalation device and the drug formulation.**
- **Having the ability to produce a reproducible aerosol during both intra- and inter-exposures is pivotal in ensuring study integrity.**
- **Innovative particle engineering techniques and nanotechnology are allowing complete control over the size, shape, and chemistry of inhaled particles, enhancing formulations and improving drug delivery into the lungs.**