# Key Considerations when Repositioning a Known Drug for Inhalation Therapy

**In recent years, the pharma industry has seen significant growth in finding new uses for old drugs. Geraldine Venthoye, Executive Vice President Product Development, Vectura, looks at the opportunities for inhaled drugs.**

The repurposing and repositioning of existing drugs has become an increasingly common way to find new treatments in recent years. While the main purpose of this strategy in the past may have been to manage the lifecycle of a product by extending the intellectual property (IP) coverage, regulators are increasingly taking a negative view of repurposed projects whose sole benefit is IP extension. Rather, they expect there to be some form of therapeutic rationale, whether this is a new therapeutic application, or an improved method of drug delivery.

Repurposing involves taking a drug already approved for one indication and getting it approved for another. New indications are increasingly for an otherwise poorly-served, rare or neglected disease, where the potential patient population is small and there is little commercial incentive for de novo research. It might also be used for the same indication, but in a new formulation that allows administration via a different route. A repositioning project, meanwhile, might give an existing drug an improved or altered product profile, while keeping the same administration route. Drug repositioning and repurposing now accounts for almost a third of all new drug products, generating half a trillion dollars in annual sales across all dosage forms.[1] Either way, there are advantages both for patients and for innovators.

For innovators, any drug repurposing or repositioning programme will need to offer a compelling commercial case. Every company will have a proprietary method for determining which potential projects are worth pursuing, but the broad principles are the same: decide whether there is an unmet clinical need, whether there is space in the market, and whether the potential revenues are likely to be sufficiently high to cover the development outlay with a decent return on investment.

### Inhaled Drug Opportunities

A reasonable starting point for the number of potential repositioning and repurposing projects that might successfully use inhaled delivery would potentially be around 300. Discounting those that do not fit with a company's existing R&D strategy will typically reduce the list by about two-thirds, leaving at least 100 projects on the longlist (see Figure 1). The next step is to consider the potential for meeting clinical needs and filling a gap in the market. It is crucial that there should be a compelling scientific rationale for the new application; if it fulfils a true unmet medical need, then the project passes on to the next stage of the triage. But even if it does not meet this criterion, if the patient population is sufficiently large, and the disease sufficiently widespread, there may still be a place for it in the market alongside existing products, particularly if there is the prospect of an improved delivery mechanism.

Projects deemed to have clinical potential are then assessed for their commercial possibilities, including whether there would be sufficient differentiation from any competition, and how crowded the marketplace for that indication is already. The projected development timescale should also be considered; if it is too long it will have a big impact on the overall cost of the project, and the time required to recoup the costs of development may make the project unviable.

For projects that pass this hurdle, the next question is whether or not technical advantages are available. Applying proprietary technology, either from in-house or external sources, that will offer measurable improvements in functionality and performance will make the project more resistant to competition if it reaches the market, and will bring significant commercial advantages.

The final consideration is the overall feasibility of the project. There are numerous challenges involved in developing inhaled drug products, and a company needs to be certain that it has established in due diligence that it has the research capabilities required to carry the project to a successful conclusion. Advice should be sought from key opinion leaders and expert scientific advisers as to whether there may be specific challenges within the development process, and importantly, whether it is likely that the project could take advantage of abbreviated regulatory pathways.

From the original list of more than 300 potential projects, the shortlist is likely to number fewer than 10. For inhaled products in particular, technical considerations will play a huge part in whether or not the project can achieve both technical and commercial success.

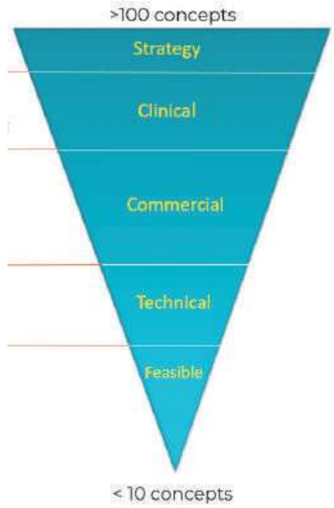



*Figure 1: Key considerations in selecting an asset to develop*

### Advantages of Repurposing or Repositioning

Repurposing or repositioning offers a number of commercial benefits. First, there is the prospect of a faster route to market than for a new molecule, as most of the necessary safety trials will already have been completed. Preclinical testing will, therefore, be limited to anything specific to a new mode of delivery and dosage level. A repurposing or repositioning can usually be completed in less than 10 years, and often significantly faster, compared with the 10–15 years that a novel API or biologic drug typically takes from initial idea to marketing approval. This reduction in time is reflected in lower costs, and the rates of attrition will be lower as so much information is already known.

Second, there may also be the opportunity to resurrect programmes that never reached the commercial phase, either because they were deemed unviable or were withdrawn and halted for a lack of efficacy in late-stage clinical trials. Some or all of the development work may well have been done, making the repurposing or repositioning route a relatively fast and low-cost way to bring the product to market.

Both scenarios can be used to extend IP coverage, driving additional revenue for innovators. For example, a drug approved for an adult might undergo repositioning for the paediatric market, which may or may not include changing the delivery mechanism, such as moving from a metered dose inhaler to a smart nebuliser or a dry powder inhaler to suit the expanded patient population. Having an effective delivery device can also provide an additional layer of market protection from competition.

Improving patient compliance may also be a source of commercial benefits for innovators; if patients take a drug correctly and therapeutic benefits are established, it is likely to be prescribed more widely. Creating novel formulations that allow for a different route of administration can improve delivery or compliance, and may also permit the treatment of further conditions. Alternatively, a new formulation may be administered via the same route, but changes or improvements to the product profile, perhaps by enabling extended release delivery, could reduce the dosage burden on the patient.

This is particularly true of inhalation drugs. Metered dose inhalers can be challenging for some patients to use correctly, because of the requirement to time the dose with breathing in, and if a patient fails to do this properly, the benefit of the drug may not be felt, leading to discontinuation of treatment. A device that removes this requirement for careful breath and dose synchronisation has compelling commercial advantages.

Modern nebulisers are not only smaller and easier to use than older models, but can also have smartphone connectivity built in, through Bluetooth, for example. This ability to monitor treatment can be invaluable, not only for compliance, but to allow physicians to keep track of how well the treatment is working. Some smart nebulisers use flow and volume control to better target the nebulised aerosol to the correct part of the lung, or within a specific type of inhalation profile. Such modern devices are designed to be breath-actuated, which means they only nebulise while the patient is actively inhaling and therefore less expensive drug is wasted.

For example, iloprost (Ventavis) is used to treat the rare, debilitating, fatal disease pulmonary arterial hypertension (PAH) and can extend life expectancy from approximately three years to 10–12 years. However, the drug needed to be dosed nine times a day via a nebuliser, and each dose took 10 minutes to administer, representing a huge treatment burden to the patient. Repositioning the drug to be delivered by an advanced smart nebuliser has allowed the dosing time to be reduced from ten minutes to three minutes. Although this must still be done up to nine times a day, it marks a substantial improvement in the patient's quality of life. The device also gives the patient feedback, leaving them feeling more in control of their treatment and their disease.

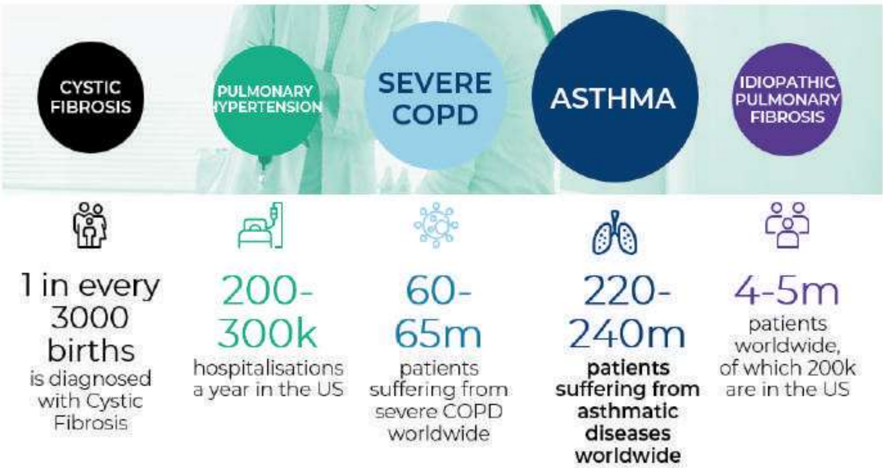
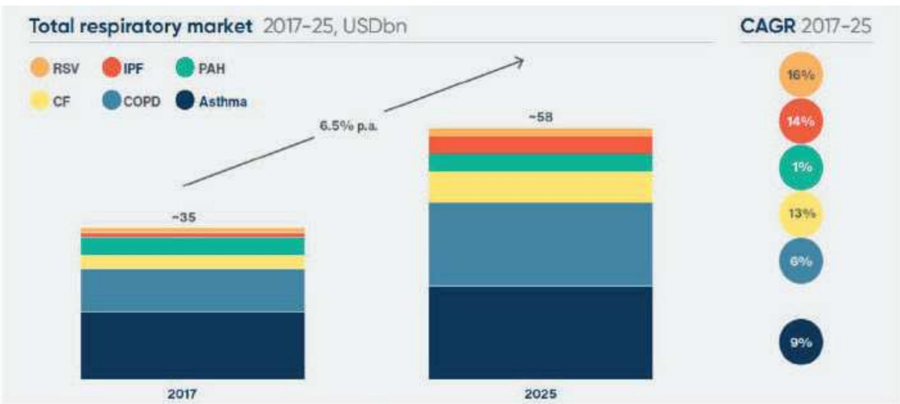



*Figure 2: Sales growth in the respiratory market [source: WHO, British Lung Foundation, GSK, BI]*




Abbreviations: IPF- Idiopathic Pulmonary Fibrosis; CF- Cystic Fibrosis; RSV-Respiratory Syncytial Virus; PAH- Pulmonary Arterial Hypertension
1 Other includes biosimilars, new derivatives, new drug application (NDA) SOURCE: Evaluate Pharma, including biologics

*Figure 3: Total respiratory market 2017-25*

**Unmet Market Needs**

There are a significant number of unmet clinical needs in respiratory medicine, besides PAH, that make the global respiratory market an attractive proposition for repurposing and repositioning drugs. These conditions include not only asthma and chronic obstructive pulmonary disease (COPD), which together comprise more than half the whole market value for inhaled products, but also more niche diseases such as cystic fibrosis (CF), pulmonary hypertension and idiopathic pulmonary fibrosis (see Figures 2 and 3). And although there have been significant advances in treatment for CF in recent years, these are effective only in a small sub-population of patients. Despite this, CF is outstripping the market with an annual growth rate of 10%, against a background of 6% growth overall.

These conditions may only have small patient populations, but they represent high-value opportunities. Furthermore, if a project is given orphan drug status, it may qualify for abbreviated approval processes and fast-track designation, as well as financial incentives such as fee waivers and tax credits, and even extended exclusivity, which is particularly important for a repurposed product.

Inhalation is most familiar as a route for administration for diseases and conditions that directly affect the lungs, including opportunities to develop combination products whereby two APIs are dosed together. One example is GSK's inhaled combination asthma product, Trelegy Ellipta, which treats COPD patients with a corticosteroid, a long-acting muscarinic antagonist as well as a long-acting beta agonist simultaneously.

Delivering drugs systemically via the lungs can also be of benefit. Inhaled delivery offers fast onset of action: a drug absorbed deep within the lungs can be taken up by the bloodstream almost as quickly as one that is injected subcutaneously. This extremely rapid onset of action would be hugely beneficial for time-sensitive applications such as pain relief, migraine treatment, or even schizophrenia. It can also be possible to dose within tight therapeutic windows, or to mimic the pharmacokinetic profiles that are achieved with more invasive delivery routes such as injection. Inhaled administration can also be potentially used to effect mucosal vaccination.

Inhalation also has a major advantage over oral administration, as the drug avoids the first pass metabolism of the liver. This can prevent the formation of problematic metabolites, which may cause undesirable side-effects, and can also be advantageous if the drug is susceptible to being broken down by digestive enzymes in the gut.

Some drugs that use the lungs for systemic delivery have already reached the market, including levodopa, used to treat Parkinson's disease, and MannKind's inhaled insulin product, Affrezza, although take-up of the latter has been limited.

**Future Opportunities**

The repurposing and repositioning of existing drugs for new applications is becoming increasingly appealing, given the escalating cost, risk and time involved in de novo development. While there is significant unmet medical need in conditions affecting the lung, both common and rare, there are other opportunities for harnessing inhalation technologies for systemic delivery and for combination drug products. Combining a differentiated enabling technology with an expedited approval pathway can provide both a rapid route to market and the concomitant commercial benefits to the pharma company, and, more importantly, significant benefits to patients.

**REFERENCES**

1. Naylor, S. et al. Therapeutic drug repurposing, repositioning and rescue. Drug Discov. World Spring Edition 2015

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Dr. Geraldine Venthoye leads Vectura's Pharmaceutical Development and Medical Device Development departments, and is responsible for the strategic and technical advancement of the company's products, development services and technology platforms. She joined Vectura in June 2016 upon completion of the merger with Skyepharma PLC, where she had been executive vice president pharmaceutical development since 2013, having joined Skyepharma as head of the inhalation business unit in September 2003. Dr. Venthoye is a UK registered pharmacist and holds a doctorate degree in pharmaceutics from the University of London.