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DRUG REPURPOSING – BROADENING PATIENT ACCESSIBILITY VIA A CHANGE IN DRUG DELIVERY SYSTEM

In this article, Badre Hammond, Associate Director, Market Development, Geralt Williams, PhD, Director, Scientific Affairs, and Herve Pacaud, Business Development Director, all of Aptar Pharma, discuss the growing trend of repurposing, whereby an existing drug product is reformulated for a new route of administration and/or therapeutic area, with a particular eye on the advantages of repurposing for the nasal route.

New chemical entity (NCE) development and commercialisation requires 10 to 15 years of development and represents around US$2.6 billion (£1.9 billion) in investment.[1] The huge scale of this requirement has led to a growing trend towards repurposing already existing molecules.[2] These developments are often undertaken by smaller technology companies and start-ups that are looking to explore new markets and new therapy areas.

For clarification, when we talk about repurposing, we mean the process by which pharmaceutical companies can leverage an existing drug and reformulate it by finding new routes of administration, new indications or new therapy areas. By doing so effectively, a whole spectrum of new lifecycle management opportunities can be opened up. Larger pharmaceutical companies have also recognised the benefits of drug repurposing, in particular in the use of nasal products to treat central nervous system (CNS) conditions.

Why repurpose? The reasons for drug repurposing are many and varied, but the bottom line is that a reduced development time, and therefore significantly lower development costs, can only be good news for patients. This enables both large pharmaceutical companies and smaller organisations to be more agile and innovative in discovering new therapies with much less of the inherent cost/time risk associated with NCE development.

The combination of reduced development time/cost and lower regulatory risks makes repurposing a truly affordable, realistic and achievable opportunity. Ideally, this translates into more therapies getting to market faster and cheaper.

In this article we will explore the rise of drug repurposing with a particular focus on the repurposing of drugs for nasal drug delivery.

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CLEAR BENEFITS FOR PATIENTS

The majority of drug repurposing projects Aptar Pharma has participated in have resulted in a nasal device being the administration route of choice. Why is this? Primarily because of greater patient convenience and improved user compliance, but also to circumvent particular objections to certain delivery routes. For example, patients may suffer from needlestick anxieties or tablet forms may make them feel nauseous.

There are other, very practical reasons to select nasal drug delivery as the administration route. If we consider Aptar Pharma's Unit Dose System (UDS) technology, it enables the systemic delivery of drugs without the need for injection. That means the patient does not need a healthcare professional to administer the drug, which is much more convenient for them and lowers overall cost to the healthcare system.

As another example, consider an emergency scenario where the patient has fainted or is unconscious. With a nasal spray, essentially anyone can be of assistance in administering the product. This is certainly the case for Adapt Pharma (Radnor, PA, US), whose nasal naloxone product, Narcan®, utilises UDS technology (Figure 1).

A SIGNIFICANT OPPORTUNITY

If we subscribe to Eroom's law – despite improvements in technology, drug discovery is actually becoming slower and more expensive over time – NCE development cannot be the only focus for pharmaceutical and biotechnology companies in the future, particularly in the context of the investment and resources required, coupled to the very real risk that the product may never see commercial launch.

It is estimated that a grand total of approximately 3,250 drugs have been approved in at least one country.[3] This represents a significant opportunity if some of these can be repurposed for other specific therapies, particularly when considering that the anticipated development time can be cut by two thirds and the level of investment is substantially lower too, perhaps even as little as $20 million[4] compared to the $2.6 billion price tag of an NCE.

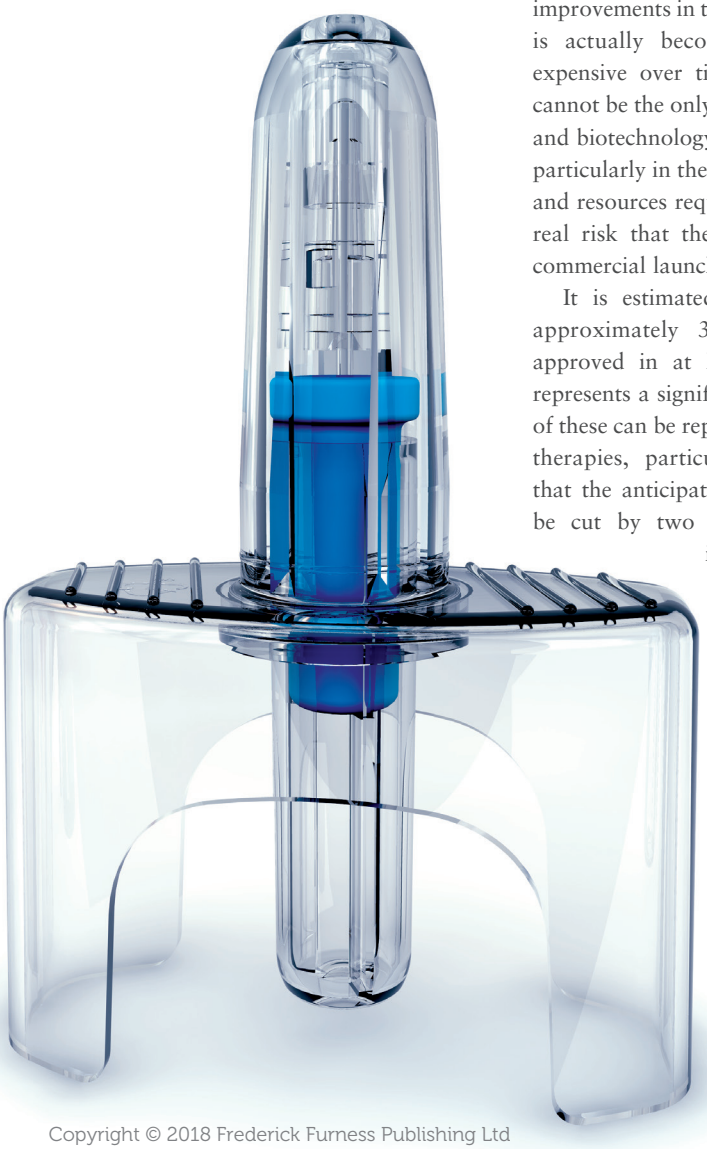

Figure 1: The Unit Dose System (UDS) single shot nasal drug delivery technology from Aptar Pharma is utilised in Adapt Pharma's Narcan® nasal spray.

NEW LIFE FOR EXISTING PRODUCTS

Repurposing an existing marketed drug product can also bring real added value to pharmaceutical companies by complementing existing ranges of products and increasing market share. In order to harness the total value of a drug product, nasal delivery devices, with their established technology and well-documented regulatory guidelines, can be useful lifecycle management (LCM) tools. The concept of an LCM strategy is not new. In fact, in 2014 50–60%[5] of drugs or biologics approved or launched for the first time in the US were either existing drugs repositioned for new indications, reformulations or new combinations of existing drugs.

Let us examine the case of naloxone nasal spray as an example of how repurposing can be done both efficiently and effectively. Naloxone is a competitive antagonist to opioids in the CNS and has been approved for the treatment of opioid overdose as a prescription medication in the US since 1971.

Access to naloxone has been extended to home use through the prescribing of off-label injectable naloxone, which combines a prefilled syringe with a mucosal atomisation device for intranasal spray administration. The widening of this off-label practice suggested that there was an unmet medical need for a patient-friendly method of naloxone administration.

The parenteral dose was 0.4 mg, although several doses could be administered to address an opioid overdose crisis. A nasal formulation and device has since been developed by Adapt Pharma (Narcan®) using the Aptar Pharma UDS device at 2 mg and 4 mg per spray. This repurposed product was approved in Europe in 2017 and in the US in 2015.

THE 505(B)(2) PRODUCT REGISTRATION PATHWAY

The 505(b)(2) pathway is designed to allow the approval of a drug which isn't new but differs in several meaningful aspects. The US FDA guidance explains that it was created with the intent "to encourage innovation without creating duplicate work and reflects the same principle as the 505(j) application: it is wasteful and unnecessary to carry out studies to demonstrate what is already known about a drug".[6]

Importantly, the regulators offer a market exclusivity period of three years to products approved using this pathway,

compared with 180 days for a purely generic formulation. Equally important, IP challenges are minimised because a repurposed drug is a distinct offer, as opposed to a generic.

CHALLENGES YET REMAIN

Repurposed drugs still must make it through Phase II and III clinical trials for their new purpose. Naturally, such trials eliminate a significant number of compounds that make it that far.

Let us return to our nasal delivery example. Nasal drug delivery can be a challenge and several hurdles may have to be overcome. Reformulation, optimising pk performance, coupling the formulation with the right drug delivery device and selecting the right regulatory pathway are all challenges that may be faced when developing suitable formulations.

In specific respect to nasal applications, the repurposing of an approved drug requires consideration of certain elements, including molecular weight, charge and lipophilicity, which will strongly influence eventual local action or absorption. The technical and regulatory expectations for nasal and sublingual sprays have evolved over the past few years.[7-8] Parameters such as droplet or particle size distribution, spray pattern, dose content uniformity and extractable and leachable profiles are now common expectations for the regulatory dossiers.

A PROVEN APPROACH

Table 1 shows several clear examples of drugs that have successfully been repurposed to nasal delivery. With the exception of nicotine, all of the drugs referenced were or are available as an injection.

There is also a considerable pipeline of repurposed projects, as shown in Table 2,

> "In order to successfully repurpose a drug for nasal delivery, pharmaceutical companies must select a device partner that can clearly demonstrate capabilities and experience in the development of spray technology."

> "Importantly, the regulators offer a market exclusivity period of three years to products approved using the 505(b)(2) pathway, compared with 180 days for a purely generic formulation."

which adds further credence to the argument that repurposing is a sustainable and attractive proposition for patients and pharmaceutical partners alike.

PARTNERING WITH APTAR PHARMA

In order to successfully repurpose a drug for nasal delivery, pharmaceutical companies must select a device partner that can clearly demonstrate capabilities and experience in the development of spray technology. They should also have demonstrable experience in helping partners navigate the 505(b)(2) pathway to compliance.

As a trusted partner to the pharma community, Aptar Pharma offers a comprehensive portfolio of specialised drug delivery devices, components and services, all designed to enable the success of our customers. Recognised and respected globally for our proven regulatory expertise, we simplify and accelerate our partners' path through approval and compliance processes.

This experience, expertise and global footprint of resources (including Aptar Pharma's specialist company, Next Breath, an intellectual leader in the field of inhalation and nasal spray development,

INN (Nasal Brand, Manufacturer)	Therapeutic Applications
Desmopressin (Minirin, Ferring)	Bedwetting
Testosterone (Natesto, Acerus)	Hormone replacement therapy
Nictoine (Nicorette, Pfizer)	Smoking cessation
Fentanyl (Instanyl, Takeda)	Pain management
Ketorolac (Sprix, Egalet) (non-narcotic analgesic)	Pain management
Naloxone (Narcan, Adapt)	Opioid overdosing
Nafarelin (Synarel, Pfizer)	Endometriosis
Sumatriptan (Imigran, GSK)	Migraine

Table 1: Drugs successfully repurposed for nasal delivery.

Examples of Drugs in Development/Clinic for CNS/Brain	Therapeutic Applications
Diazepam	Epilepsy
Glucagon	Diabetes, hypoglycaemia
Hypocretin-A	Narcolepsy
Insulin	Alzheimer's
Ketamine	Depression
L-dopa	Parkinson's
Octreotide	Acromegaly
Olanzapine	Bipolarism
Oxytocin	Autism

Table 2: Drugs presently being investigated for nasal delivery.

testing and regulatory strategy) has enabled us to develop a complete services package which includes support in R&D, solution development, device realisation and regulatory submission. This focus has delivered results. In the past five years, Aptar Pharma's regulatory and development teams have supported 35 INDs, 31 NDAs and 55 ANDAs in the nasal space alone.

CONCLUSION

There are many and varied reasons why a pharmaceutical company would consider drug repurposing as a viable option. The significantly reduced development time and, therefore, lower development costs mean that more therapies get to market faster, cheaper and with reduced risk than would otherwise be the case, ultimately benefitting patients and the healthcare system overall.

Very often in our experience, repurposing results in a nasal drug delivery system which offers many patient benefits in terms of convenience, ease of administration and efficacy. Critically, it also negates the need for intervention from a healthcare professional.

Repurposing is not plain sailing and companies should be mindful to select a drug delivery systems partner that has a proven track record in repurposing. They should be able to demonstrate the necessary validation services and be able to guide through the regulatory process seamlessly. If they can do that, then repurposing could be a perfect opportunity.

ABOUT THE COMPANY

Aptar Pharma provides innovative drug delivery systems, components and services to pharmaceutical, consumer healthcare and biotech customers worldwide, spanning a wide range of routes of administration, including nasal, pulmonary, ophthalmic, dermal and injectable. Aptar Pharma's mission is to provide complete solution services built around its drug delivery systems and to create stage-specific development packages designed to proactively address regulatory needs and accelerate approval. Overall, six billion components and systems are produced annually across 11 manufacturing sites and are accessed by 1.6 billion patients, and over US$50 billion worth of pharmaceutical products depend on Aptar Pharma's systems. Aptar Pharma is part of AptarGroup, Inc (NYSE:ATR).

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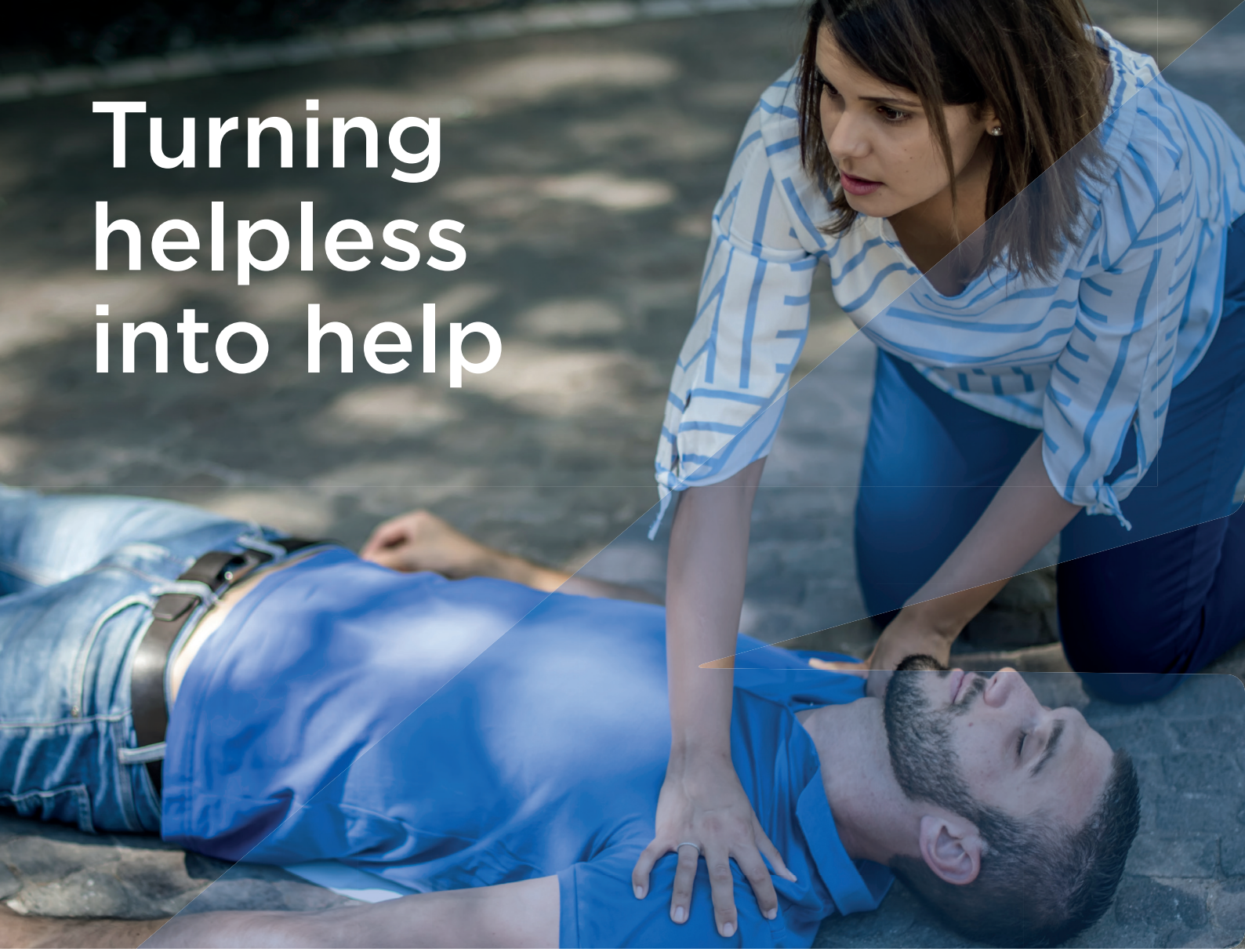
ABOUT THE AUTHORS

Badre Hammond is Associate Director, Market Development, at Aptar Pharma, with a background in biochemistry and 14 years' experience in pharmaceutical product development focusing on nasal and pulmonary drug delivery systems. Mr Hammond has broad experience in managing development of novel drug product programmes for the pharmaceutical market from formulation development, preclinical, CMC, to clinical phase.

Dr Gerallt Williams is Director, Scientific Affairs, Prescription Division, at Aptar Pharma. After obtaining his PhD from the University of Wales (UK) in 1985, Gerallt has held various industrial positions at Monsanto Inc (UK), Fisons Ltd (UK), Valois (France) and Inhale/Nektar Therapeutics (US). Dr Williams is now in charge of scientific affairs for the Aptar Pharma prescription division in Le Vaudreuil, France, and is engaged in the development of new devices for nasal, inhalable and injectable drug products.

Herve Pacaud is Business Development Director at Aptar Pharma and has more than 25 years' experience in devices for drug delivery via the nasal and buccal routes. After graduating in Sales and Marketing at the University of Amiens (France), Herve held different positions in the automotive industry and then at Valois, now Aptar Pharma. At Aptar Pharma, Mr Pacaud has worked in various sales and business development positions in Europe and Asia. Based in France, he now has the global responsibility for business development for allergic rhinitis, vaccines and CNS applications.

Turning helpless into help



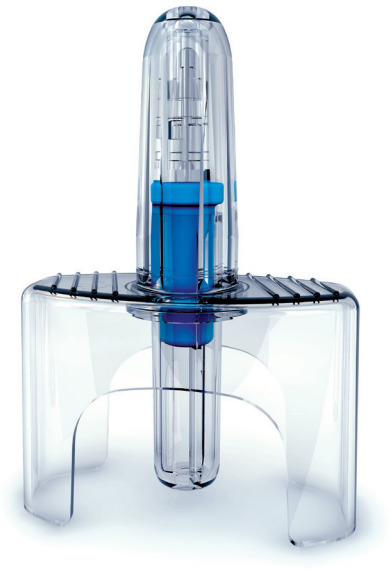
Unit Dose System, the single shot nasal drug delivery device from Aptar Pharma

You may recognize our UDS as the delivery device for NARCAN®, the first and only FDA-approved nasal form of Naloxone, used for the treatment of an opioid emergency. What you may not recognize is that there is so much more to this device than just for emergency situations.

UDS was designed to enable the systemic delivery of drugs without the need for injection or administration by a healthcare professional. Primeless, with one-handed actuation and 360˚ functionality, this device is approved with multiple drug products by the FDA and is used by thousands of people every day in a range of scenarios from migraine medication through to breakthrough pain relief in end-of-life situations.

All delivered with the certainty of science and safety you'd expect from Aptar Pharma, one of the world's leading providers of drug delivery systems.

To find out more about how Aptar Pharma can help you make a positive impact on patients' lives, call **Herve Pacaud**, Business Development Director at Aptar Pharma on **+33 1 3917 2020** or email **herve.pacaud@aptar.com**



Delivering solutions, shaping the future.

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