



Repurposing medicines: the opportunity and the challenges

Unlocking game-changing benefits for patients



LifeArc

LifeArc is a self-funding charity focused on improving the lives of patients. We drive medical innovation through our own research and our work with a range of partners from industry, charities, universities and research organisations. We focus on translation - progressing work from early lab-based findings through to development and a point where it can be used in patients.

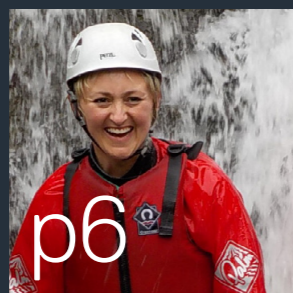


Pinsent Masons

Pinsent Masons is a full service multinational law firm operating out of 26 locations across four continents. Their international life sciences practice, comprising more than 100 senior sector specialists, many of whom are leading individuals in their field with relevant scientific degrees (some to PhD) and experience drawn from industry, is dedicated to helping clients continue to develop cutting-edge strategies that support the development of, and patient access to, medicines.

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Case study: LAM

How effective repurposing has helped women with a rare lung disease worldwide.



Case study: Myotubular Trust

Find out how the breast cancer drug tamoxifen could help boys with a rare genetic condition.



Case study: IntraBio

Investigating a vertigo drug as a treatment for inherited neurodegenerative diseases.

Finding new uses for existing medicines

Drug repurposing offers a potentially rich source of safe and effective therapies for both common and rare diseases. The benefits include the possibility of lower overall development costs and shorter timeframes for getting life-changing treatments to patients.



Improving awareness of the challenges and finding ways to overcome them will help to improve the likelihood of potentially life-changing medicines reaching patients in the clinic.

Dr Melanie Lee, CBE
CEO – LifeArc

Drug repurposing has experienced recent success in the fight against COVID-19. For example, tocilizumab, originally an arthritis drug, was discovered as an effective treatment for hospitalised patients – typically in addition to dexamethasone, another repurposed drug shown to have life-saving benefits.

But while these high-profile success stories provide a catalyst for unlocking the full potential of drug repurposing, significant challenges remain.

Due to the potentially lower costs involved, there is significant interest from academics, patient groups and charities who can play a major role in driving repurposing opportunities. The approach is often particularly attractive for rare diseases where the high costs and risk of failure can make traditional drug discovery commercially unviable for industry.

However, in our experience, charities and researchers can often be naive to the commercial and regulatory challenges when submitting applications for drug repurposing projects. Improving awareness of the challenges and finding ways to overcome them will help to improve the likelihood of potentially life-changing medicines reaching patients in the clinic.

To help charities and researchers devise their own strategies to repurpose drugs we held a seminar, in partnership with Pinsent Masons, to examine the path to treatment.

The virtual event, which focused on addressing the opportunities and challenges of repurposing drugs for patients with diseases that are poorly treated with current therapies, was held on 9th March 2021. We were delighted to welcome more than 150 attendees – highlighting the enormous interest in the topic.

I feel incredibly optimistic about the future for drug repurposing. Although the route to patients is not always clear, I hope you will find the case studies inspiring. These examples show how recycling existing medicines can make a huge difference to people's lives – especially for those living with rare diseases.



Our definitions

We have used the following terms throughout this report:

Indication

– a specific licensed clinical use of a drug.

Marketing authorisation

– licensing from the relevant regulatory authority for use of a medicinal product for a specific indication.

Conditional marketing authorisation

– a pragmatic tool for the fast-track approval of a medicine that fulfils an unmet medical need.

Drug repurposing

– a new use for an existing drug in an indication that is outside the scope of the original indication.

Off-label use

– where a medicine is prescribed outside the scope of its marketing authorisation.

Patented products

– only the company that owns the patent can manufacture and market the product either doing so itself for the life of the patent, or by licensing to others.

Generic drugs

– contain the same active ingredient as the equivalent original branded product and can be produced by other companies once the originator's patent and regulatory protection periods have expired.

Biosimilar medicines

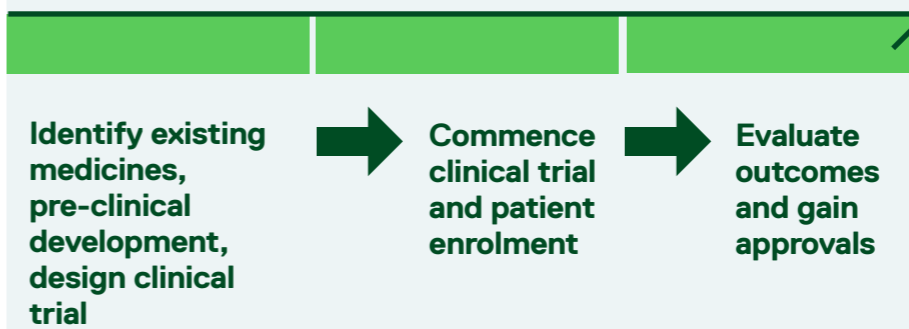
– highly similar and clinically equivalent to an existing biological medicine (which are very complex, protein-based medicines) after the original patent and regulatory protection periods have expired.

Drug repurposing for rare diseases

Compared to developing an entirely novel compound, drug repurposing offers huge potential for new treatments to reach patients faster. A big advantage is that an existing medicine may have a well-established safety profile, which can help to reduce the development time and costs.

Drug repurposing time frames

Typical time frame – **1 to 3 years**



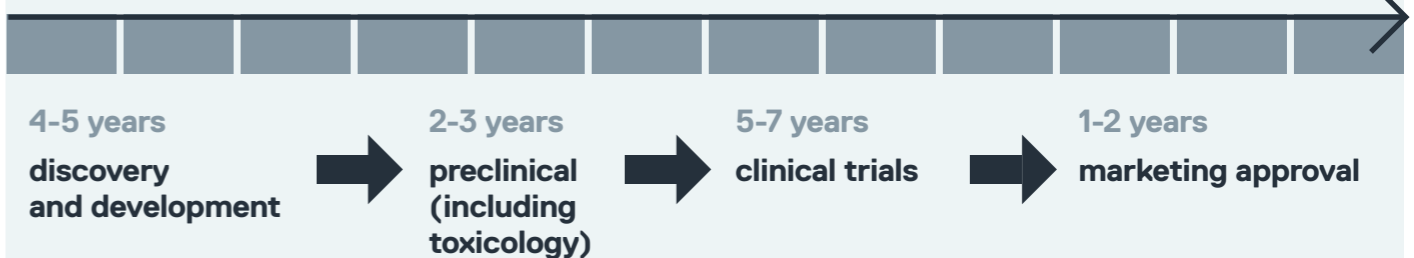
While nearly 8,000 rare diseases have been identified, only around 5% have licensed treatments. As many are life-threatening conditions, there is an urgent need to find effective new treatments for patients.

Developing one successful medicine can take over a decade and cost more than \$1 billion. It can be even more challenging for rare diseases, due to small patient populations and the high costs of research.

Drug repurposing offers exciting opportunities to accelerate the development of new medicines for rare diseases. The approach offers several advantages over traditional drug discovery - with fewer risks, lower costs and shorter timeframes. But it also has potential challenges, including legal and regulatory issues and the feasibility of clinical trials.

Standard novel drug development time frame

Typical time frame – **average 12 years**



Advantages of drug repurposing

- ✓ Reduced risk of failure as safety and dosing profile typically well established
- ✓ Product manufacturing and supply chains already available
- ✓ Patients are often more willing to take part in clinical trials due to the appeal of the 'known' factor
- ✓ Faster development times and reduced costs

Potential challenges

- ? May need to fill in the gaps on safety, exposure & preclinical data on the mechanism of action
- ? Identifying the optimal drug & formulation
- ? Feasibility of clinical trials given unlicensed/off-label access
- ? Existing intellectual property (IP)/patents on product

Potentially ‘game-changing’ benefits for patients with rare diseases

Jo Pisani, a LifeArc Trustee, shared an impressive story of how drug repurposing has transformed the outlook for women with a rare progressive lung disease around the world.



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The average age of onset of LAM in patients in the United Kingdom

Lymphangioleiomyomatosis (LAM) is a rare condition that affects almost exclusively women of childbearing age. While the condition mainly affects the lungs, it may also involve the kidneys and lymphatic system.

In people with LAM, abnormal smooth muscle cells (LAM cells) start to grow in certain organs or tissues, particularly in their lungs, lymph nodes and kidneys. Over time, the abnormal growth and movement of LAM cells can damage healthy lung tissue, causing holes or cysts, preventing oxygen from getting to the rest of the body.

Symptoms of LAM include breathlessness, tiredness, coughing and bleeding around the kidneys. If left untreated, the condition can cause serious and life-threatening complications.

LAM is a progressive disease, but how quickly it worsens varies from person to person. Before 2015, lung transplantation was the only approved treatment option for women with severe disease.

Repurposing rapamycin for LAM patients
Rapamycin (also known as sirolimus in the clinic) is a natural product first isolated from bacteria in a soil sample from the island of Rapa Nui.

Researchers subsequently discovered that rapamycin exhibits several properties, including immunosuppressive effects - which ultimately led to its approval as a treatment for kidney transplant patients.

Further laboratory research revealed that the drug inhibits cell growth by targeting the mTOR cellular pathway, which plays a key role in cell growth, survival and movement.

Scientists discovered that LAM is caused by faults in the *TSC1* and *TSC2* genes that encode proteins involved in the mTOR pathway. Laboratory studies showed that LAM cells have overactive mTOR signalling and rapamycin can slow down cell growth. These data indicated that rapamycin could be an effective way to slow down the progression of the disease in LAM patients.

Following the encouraging results of an early-phase clinical trial in the UK, an international, randomised, placebo-controlled trial (the MILES trial) was set up to find out if rapamycin could benefit patients with LAM. The impressive results showed that the drug was safe and effective for LAM patients - stabilising lung function and improving their quality of life.

Rapamycin is now the standard of care for women with LAM. In most cases, taking the drug has replaced the need for lung transplantation, transforming the lives of women living with the condition.

"Rapamycin is an example of successful repurposing - it's almost a wonder drug for women with LAM," said Jo.

Changing lives

Sarah Sharples (pictured above) is 40 years old and was diagnosed with LAM ten years ago. Before going on rapamycin, her lung function had been slowly declining and she was struggling to stay awake past 7pm. She thought she would have to reduce her hours at work and couldn't carry out a lot of her usual activities. But her life has hugely improved since starting on rapamycin around five years ago.

"Combined with inhalers, taking rapamycin has ensured that I can take part in all the activities I enjoy. I've been able to keep working full time and, most importantly, I can keep up with my daughter!"



Combined with inhalers, taking rapamycin has ensured that I can take part in all the activities I enjoy.

Sarah Sharples, LAM patient

A brief history of Rapamycin

1972

Rapamycin was discovered from a soil sample from Rapa Nui. Subsequent laboratory studies revealed several properties, including immunosuppressive effects.

1990s-2000s

Basic research uncovers that rapamycin inhibits the mTOR signalling pathway. Faults in *TSC1* and *TSC2* genes, encoding proteins involved in the same pathway, are identified in LAM patients.

1999

Rapamycin receives marketing authorisation from the US Federal Drugs Administration (FDA) as an immunosuppressant for kidney transplant patients.

2001

Rapamycin receives marketing authorisation from the European Medicines Agency (EMA) as an immunosuppressant for kidney transplant patients.

2004-2006

Early-phase trial involving patients with LAM in the UK.

2006-2010

A randomised placebo-controlled clinical trial involving 89 patients with LAM in the USA, Canada and Japan (the MILES trial).

2011

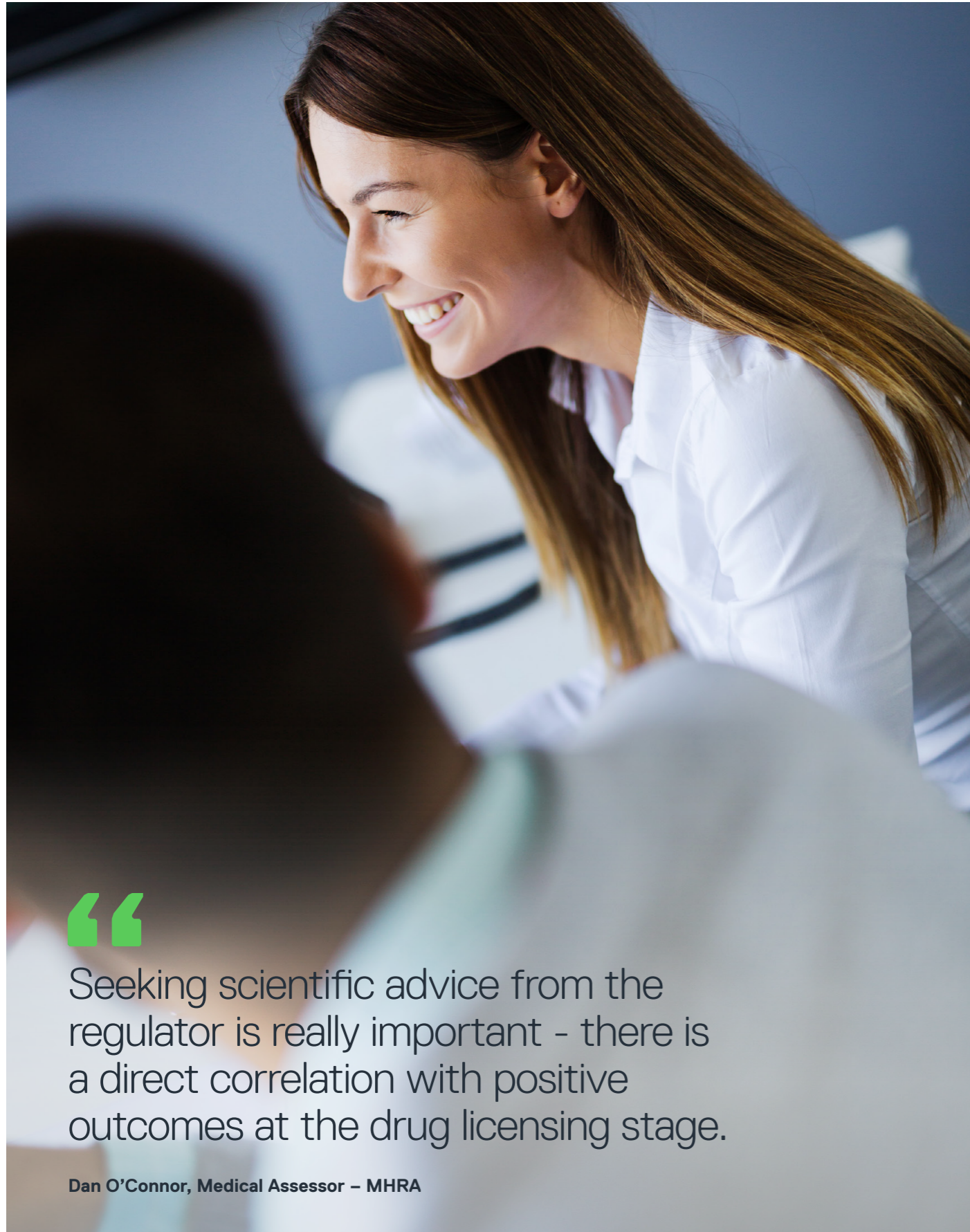
Clinical trial results published, showing rapamycin is a safe and effective treatment for LAM patients.

2015

FDA licenses rapamycin for the treatment of LAM.

2018

EMA licenses rapamycin for the treatment of LAM.



Seeking scientific advice from the regulator is really important - there is a direct correlation with positive outcomes at the drug licensing stage.

Dan O'Connor, Medical Assessor – MHRA

Working in partnership with the regulator

All drugs require a marketing authorisation before they can be placed on the market. Many panellists emphasised the benefits of seeking regulatory advice at any stage of drug development, but particularly at the outset.

Dan O'Connor, a Medical Assessor at the Medicines and Healthcare products Regulatory Agency (MHRA), highlighted that seeking scientific advice from the regulator is standard practice for commercial companies but is currently under-used by academics and charities. He said: "Seeking scientific advice from the regulator is really important – there is a direct correlation with positive outcomes at the drug licensing stage."

About the MHRA

The Medicines and Healthcare products Regulatory Agency (MHRA) regulates medicines and medical devices, and blood components for transfusion in the UK, responsible for ensuring their safety, quality and effectiveness.

Recognised globally as an authority in its field, the agency plays a leading role in protecting and improving public health and supports innovation through scientific research and development.

In her talk, Anne Lennox, Founding Trustee of the Myotubular Trust, said that one of the very best experiences of their repurposing journey was the early and open conversations they had with the MHRA. She said: "It absolutely felt like a partnership. I can't imagine having the confidence to be where we are now if we hadn't had that early conversation."

How do I engage with the MHRA?

Scientific advice can be sought from the MHRA at any stage of the development of a medicine. The process involves an application via a request form, followed by a face-to-face meeting with MHRA experts.

The scope of the questions should address specific scientific issues in a comprehensive briefing document:

- **Quality aspects** – e.g. chemical, pharmaceutical and biological testing
- **Non-clinical aspects** – e.g. toxicological and pharmacological testing
- **Clinical aspects** – e.g. endpoints, trial duration, target population, choice of comparator, etc

The final advice is provided in a written MHRA formal advice letter. It is not legally binding for any future application of the product, either on the part of the MHRA or the organisation that is seeking advice. You can find out more about how to get scientific advice from the MHRA at: www.gov.uk/guidance/medicines-get-scientific-advice-from-mhra

How do I get a drug licensed for a new purpose?

Drug licensing is the process of evaluation undertaken by the MHRA to ensure patients receive medicines that are of suitable quality, safety and effectiveness.

Different routes are available for licensing repurposed medicines. It is possible to 'vary' an existing drug licence in a simple and quick process called a Type II variation (which can only be initiated by the licence holder). Alternatively, there is the opportunity to seek a new marketing authorisation but this is longer and more expensive than a variation. Some regulatory incentives support repurposing, such as additional periods of market protection and orphan designation.

Dan drew particular attention to the MHRA's new Innovative Licensing and Access Pathway (ILAP), which launched in January 2021. It aims to reduce the time to market for innovative treatments that meet specific criteria, such as treating life-threatening conditions or rare diseases or where there is significant patient need. The ILAP provides opportunities for enhanced regulatory and other stakeholder input. Repurposed medicines are included in the scope of ILAP.

You can find out more about the ILAP and how to apply for an Innovation Passport at: www.gov.uk/guidance/innovative-licensing-and-access-pathway

ILAP overview:

Innovation Passport

A new medicine designation links to the development of a roadmap to patient access

Target Development Profile (TDP)

creates a unique UK roadmap, using tools from a toolkit and providing a platform for sustained multi-stakeholder collaboration

A toolkit

tools are intended to drive efficiencies in the development programme, supporting data generation and evidence requirements

An integrated pathway

pulls together expertise from MHRA, NICE and Scottish Medicines Agency (SMC) and partners in the wider healthcare system including the NHS in England and Scotland

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Tom died just before his fourth birthday. I would have given anything at all for even a five percent improvement in his strength, as that might have been just enough for him to survive. It might have made all the difference.

Anne Lennox, Tom's mother and Trustee of the Myotubular Trust

Repurposing tamoxifen for myotubular myopathy: the story so far

Anne Lennox, Founding Trustee of the Myotubular Trust, shared how disease-specific patient organisations can play a major role in driving drug repurposing opportunities.

X-linked myotubular myopathy is a rare genetic neuromuscular disorder that affects mainly boys. A child born with the condition will experience muscle weakness in all the voluntary muscles of the body. Many will develop life-threatening complications due to problems with the muscles involved in breathing and swallowing. Sadly, there is no cure - and many children will lose their lives at a young age.

Reflecting on her own experience of losing a child with the condition, Anne said: "Tom died just before his fourth birthday. I would have given anything at all for even a five percent improvement in his strength, as that might have been just enough for him to survive. It might have made all the difference."

What is tamoxifen?

Tamoxifen is a breast cancer drug that works by blocking the action of the hormone oestrogen. It was first approved in the 1970s and has since benefited millions of women and men with the disease around the world. The drug is also used to treat boys with certain hormonal disorders. It is taken as a pill and has a good safety profile.

Following a serendipitous laboratory discovery, the Myotubular Trust has played a central role in driving progress towards an early-phase clinical trial to evaluate the merits of tamoxifen as a treatment for myotubular myopathy.

<20%

The percentage of boys affected with X-linked myotubular myopathy who make it to adulthood

The key role of patient organisations in repurposing

- ✓ Funding opportunities for the 'right question' to be asked
- ✓ Helping to keep focus on impetus
- ✓ Funding to remove bottlenecks identifying where things are slowing down and helping put solutions in place, speedily
- ✓ Moving working model to supportive networks of key players
- ✓ Asking the questions; telling the real-life story
- ✓ Being the voice of the 'left behind' community with a rare condition

The study aims to recruit at least 16 children with the condition at four centres in Canada, the USA and the UK and will assess the safety and efficacy of tamoxifen over two years.

What is the appeal of repurposing for patients with rare diseases?

- The appeal of the 'known' factor - treatments with established safety profiles
- Recruiting people to take part in clinical trials is simpler - which can often be challenging for rare diseases
- Regarded as lower risk than novel therapies - especially considering tragic outcomes from recent gene therapy trials
- Outcome measure perspective - often a misconception that patients only want to find cures
- Benefit horizon is nearer - more likely that the rewards from a repurposing opportunity may happen sooner
- Equality of access - more likely to be available to more patients, which is especially important for rare disease communities

A timeline of the events leading to a clinical trial looking at tamoxifen as a treatment for myotubular myopathy

- 2014** The Myotubular Trust fund a laboratory study led by researchers in Canada to search for a compound that could reduce the levels of a fat molecule in muscle cells.
- 2015** The researchers make a serendipitous discovery showing that tamoxifen can help improve muscle strength. Around the same time, the drug also shows promise as a treatment for another genetic muscle-wasting condition.
- 2017** The Myotubular Trust award the team another grant to carry out pre-clinical studies to determine the best dose for use in human studies. The necessary steps are also taken to set up a clinical trial in Canada.
- 2019** The clinical trial protocol is extended to the UK and funding is awarded from the Myotubular Trust and Great Ormond Street Hospital Charity.
- 2020/21** Ethical approval is confirmed, submitted to the MHRA for regulatory approval.

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Intellectual property and patents

Nicole Jadeja, Partner at Pinsent Masons, discussed the challenges and opportunities around intellectual property (IP) and patents – emphasising the importance of an IP strategy at an early stage in the process.



Drug repurposing opportunities are most often driven by serendipity and patient need rather than IP. Although patents may be perceived as a legal barrier, they can play an important role along with other incentives in getting repurposed medicines to patients – particularly by attracting an industrial partner, which can help drive a project forward and boost the likelihood that it will succeed. "If you consider IP and other incentives early in the product development strategy and get it right, it can improve the prospects of the medicine reaching patients," advised Nicole. Every drug repurposing opportunity is unique and so there is no 'one size fits all' IP strategy. But for any project it will be essential to carry out an IP search at an early stage – to find out what already exists when considering what business model to adopt in order to get the product to market.

If existing patents are in place, you may not have freedom to operate. When the patent for the original compound has expired there could be secondary patents covering specific formulations, dosage regimens or uses that you might infringe. This may present the need – or the opportunity – to enter into a licensing or collaboration agreement with a third party to develop your product.

“If you consider IP and other incentives early in the product development strategy and get it right, it can improve the prospects of the medicine reaching patients.”

Nicole Jadeja
Partner – Pinsent Masons

If the original product is off-patent, this can present other challenges from a regulatory and commercial perspective. Where there are no patents the commercial landscape may be more competitive, especially if the original product has been commercially successful, and a really compelling business case may be needed to attract a business partner. Nicole then discussed the possibility of obtaining a new patent for a drug repurposing opportunity, which may help attract an industrial sponsor. She described the current processes around getting patents for repurposed medicines as a tangled web, saying: "Obtaining patents for such products is not necessarily straightforward and neither is enforcing or navigating them, but it is not impossible."

Demonstrating that you have a clear IP strategy at the outset may make it easier to obtain crucial funding, help to get the product to market and, ultimately and importantly, meet patient need.

Top tips:

- ✓ Consider the IP landscape and do this early on
- ✓ Identify who you are likely to need to collaborate with and how IP might help that happen
- ✓ If there is no product patent, don't assume there are no secondary patents that you might need to navigate
- ✓ Don't assume that you can't obtain IP - it might be a valuable asset
- ✓ Seek advice from a patent attorney

Obtaining patent protection

<p>The opportunity In Europe and most major pharmaceutical markets it is possible to obtain patent protection for:</p> <ul style="list-style-type: none"> — New therapeutic indications for authorised drugs — New formulations, dosage or delivery for the same/different indication — New combinations of medicines — New drug and medical device combinations 	<p>The challenges The subject of any patent application must be new and inventive:</p> <ul style="list-style-type: none"> — Many potential new uses could have been reported in the literature — Clinical practice could mean there has already been off-label use for the new indication — Data is needed to support any application — Enforceability could be challenging, and the law is uncertain
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Case study

The pregabalin litigation in the UK

The recent litigation around pregabalin in the UK lasted for four years and was heavily fought over, raising key questions about whether the right incentives are in place to support the development of repurposed medicines. The English courts have recognised that the patent system is currently not perfect for this purpose, exemplified by a quote from one of the judges involved:

"An important objective of modern pharmaceutical research is the discovery of new medical uses for known molecules. This commonly involves expensive research programmes, which will not be rewarded and will therefore not happen unless patent protection is available. Patent protection for second use medical patents is, however, difficult to accommodate with the traditional scheme of patent law."

Lord Sumption, Warner-Lambert vs Generics [2018] UKSC 56

The case concerned the repurposing of pregabalin, originally authorised to treat epilepsy and general anxiety disorder, as a treatment for neuropathic pain.

The drug is one of Pfizer's best-selling products, in 2013 it achieved global sales of \$4.6 billion – \$310 million in the UK alone. The company's original patent for the drug was to treat epilepsy and general anxiety disorder. But they had also obtained a later patent for a second medical use as a treatment for neuropathic pain.

After the first patent expired, Actavis launched a generic product in the EU with a so-called 'skinny' label – the packaging and patient information only specified its use for treating the off-patent indications. The UK courts then had to decide how to ensure that these generics weren't used to treat pain – leading them to order the issuing of written prescribing instructions to all pharmacies and GP surgeries.

Subsequently, Pfizer's second medical use patent was ruled invalid because the application did not plausibly demonstrate that it could treat all types of pain – as it had only been proven to target one pain mechanism. In c.2019/20 various beneficiaries under cross-undertakings provided in respect of 'full label' injunctions and the NHS Guidance Order commenced claims for loss suffered as a result of these orders. The total value of these claims exceeds £800m, a significant proportion of which is claimed by NHS

- 2013**
— Warner-Lambert's original patent expires
- 2014**
— Warner-Lambert's data exclusivity expires
— Mylan and Actavis bring claims for revocation of a second, second medical use (SMU), patent
— Warner-Lambert sues for patent infringement
- 2015**
— Actavis launches a generic product in the EU with a 'skinny' label
— NHS ordered to issue prescribing guidance
— SMU patent held invalid
- 2016**
— Court of Appeal upholds the decision of invalidity
- 2017**
— Warner-Lambert's SMU patent expires
- 2018**
— Supreme Court finds SMU patent invalid and not infringed
- 2020**
— Multiple claims commenced against Warner-Lambert under cross-undertakings for loss suffered as a result of wrongful injunctions and NHS Guidance

England Wales and Northern Ireland (and separately, NHS Scotland) on the basis that recategorisation under the Drug Tariff and full label generic entry to the market was wrongly delayed.

While the case addresses important questions, it doesn't provide all the answers regarding the value and enforceability of second medical use patents. However, it does indicate the amount and extent of data needed to support a patent application for a second medical use, as well as guiding how it might be enforced and what protection it might offer.

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Collaborating with industry

Paul Fleming, Technical Director of the British Generic Manufacturers Association (BGMA) discussed repurposing off-patent medicines and encouraged interested parties to approach the association.



Repurposing generic and biosimilar medicines have the potential to deliver huge benefits to patients and the NHS. These medicines already exist, are very affordable, enabling maximum patient access for unmet needs.

In recent years, the BGMA has gained experience from collaborating on drug repurposing projects - and with other stakeholders and the NHS to develop models to make it as easy as possible for these medicines to reach patients. Paul reflected that "we've learned that it's more about finding ways to bring together different parts of the existing ecosystem and reassembling them in a novel way, rather than inventing a whole new system."

Paul encouraged medical research charities, patient groups, academic and clinical researchers to get involved and to do so early to maximise the opportunities available to get medicines to patients. Either if you are at the stage that you already have compelling evidence - or else you are planning further confirmatory studies; both are good times to get involved with the processes that already exist, such as going to the MHRA for scientific advice. This will provide a clear measure of completeness for the clinical evidence in support of a new indication - and importantly, it also helps ensure the planned study generates the maximum amount of useful data.

About the BGMA

The BGMA represents the interests of UK-based manufacturers and suppliers of generic medicines and promotes the development of the generic medicines industry in the UK.

A key feature of the strong generics industry in the UK is that it introduces competition to the supply of prescription medicines (when patents and/or any data or market exclusivity expire) making them more affordable to the NHS and enhancing their availability to patients.

The British Biosimilars Association (BBA) is the expert sector group of the BGMA exclusively focused on biosimilars. Members of the BBA ensure access to high-quality, safe and effective biosimilar medicines for UK patients.

80-85%

The reduction in the average cost of a generic drug vs its brand-name counterpart



We've learned that it's more about finding ways to bring together different parts of the existing ecosystem and reassembling them in a novel way, rather than inventing a whole new system.

Paul Fleming

Technical Director - BGMA

Regarding the imperative about speed, Paul explained how using the licensing system can deliver that in quite an unexpected way: "The perception might be it's rather cumbersome, it's complicated, only for the pharmaceutical industry, and difficult to navigate. But with the supportive help of other stakeholders working together, this can actually be quite a speedy route to market," he said. Adding a new indication to an existing generic or biosimilar marketing authorization can be achieved in as little as six months.

Paul concluded by expressing his excitement about the huge amount of potential that lies ahead. "We are now at the point where we're moving from looking at individual examples through to building a more supportive overall pathway. The systems are growing and coming into place to make that happen more routinely and consistently - and making it much more transparent and accessible to those working in the field. Most importantly, when thinking about generic and biosimilar medicines, this is a very cost-effective solution," he said.

David Watson, Executive Director of Patient Access at the Association of the British Pharmaceutical Industry (ABPI), discusses the industry's perspectives on repurposing medicines.



Repurposing is not a new concept for the pharmaceutical industry. Medicines bring huge value to NHS patients. Yet the development of new medicines is uncertain, costly, and involves significant rates of failure. The pharmaceutical industry produces nearly all the medicines and vaccines available to us.

Part of the normal process of developing new medicines includes looking at older medicines that may or may not be used still, and starting development again in the potential search for new uses. Repurposing increases efficiency, and medicines are generally approved sooner (3-12 years)¹. The ABPI supports the repurposing of off-patent medicines for new uses through the licencing scheme.

However, the route to take a medicine through testing in a new use and through the regulatory process has not been straightforward. The European Federation of Pharmaceutical Industries and Associations (EFPIA), together with other trade associations, patient groups and regulators from around Europe have been working together with the European Commission on a repurposing pilot project with

About the ABPI

The ABPI exists to make the UK the best place in the world to research, develop and use new medicines and vaccines. They represent companies of all sizes who invest in discovering the medicines of the future.

Their members supply cutting edge treatments that improve and save the lives of millions of people. They work in partnership with Government and the NHS so patients can get new treatments faster and the NHS can plan how much it spends on medicines.

Every day, they partner with organisations in the life sciences community and beyond to transform lives across the UK.

£4.8bn

Pharmaceutical companies invest more in R&D than any other sector in the UK economy

STAMP which aims to bring together academic researchers, companies, charities and regulators to look at new uses of older medicines, to facilitate repurposing².

Using medicines off-label

For some individual patients, there may be a clinical need to prescribe medicines off-label where no clinically appropriate licensed medicine is available for that indication. Not all diseases and conditions are currently served by a specific licenced medicine, and prescribers rightly have the flexibility to use treatment alternatives justified by the clinical and therapeutic need of the individual patient.

However, off-label and unlicensed use of medicines presents a potentially greater risk to the patient, and therefore any decision to prescribe must carefully assess the risk-benefit for the patient to be treated, in consultation with the patient. The medicine will not have gone through the same degree of regulatory review of the benefits and risks in that indication, nor, for unlicensed medicines, the supportive assessment of the quality, formulation and presentation of the medicine. The responsibility for this additional risk rests with the prescriber. The decision to prescribe off-label or unlicensed medicines should never be taken on the grounds of cost alone.

¹https://efpia.eu/news-events/the-efpia-view/blog-articles/repurposing-what-is-it-and-why-it-s-important-for-covid-19/#_ftn1

²https://ec.europa.eu/health/sites/health/files/files/committee/stamp/stamp_11_47_2_en.pdf



The ABPI supports the repurposing of off-patent medicines for new uses through the licencing scheme.

David Watson

Executive Director of Patient Access - ABPI

Drug reimbursement: ensuring drugs are available to patients

Robert Whitmore of Roboleo & Co discussed drug reimbursement, describing the process as “rather like the game of snakes & ladders” – with progress helped or hindered by events during the journey.



Developing and launching healthcare technologies is complex – and this applies not just to new innovative technologies but also to repurposing existing products, especially for rare diseases.

Dr Melanie Lee, CEO of LifeArc, had earlier touched on the importance of ensuring that drugs are made available to patients, remarking that “for patients, one of the worst things is knowing a drug is there and works but they can’t access it”.

Drug reimbursement is usually the biggest barrier to patient access. In a time where there is growing pressure on healthcare budgets, understandably there is increased scrutiny of new health technologies, their effectiveness, costs and broader impact. An economic evaluation is necessary to demonstrate their value, which will require collecting robust evidence above and beyond that needed for the marketing authorisation.

Types of evaluation

A full health technology assessment (HTA) may be required, depending on certain factors – such as the market, therapeutic category or price point. This evaluation will provide evidence to aid decision-making and developing guidance on the reimbursement and administration of new health technology in a national healthcare system. If not, a less complex assessment, such as a budget impact analysis (BIA), is usually required at a national and/or regional level to look at whether its adoption is affordable, given the resource and budget constraints of the specific context.

While repurposing off-patent drugs can help simplify these processes, challenges remain. These can include uncertainty around the evidence of the benefits of a repurposed treatment compared to the current standard of care, especially for rare diseases, along with its cost-effectiveness and affordability.

Rob advised starting to collect the information that will be necessary for an economic evaluation model at the earliest opportunity. He also emphasised the importance of engaging early with stakeholders to fully understand their specific needs. Clinical experts play a far greater role than usual in HTA decisions on rare diseases. Patient organisations can also be very influential – for example, in clinical trials recruitment and patient registries.

Working in Partnership

Collaboration between all stakeholders is the best way to create a comprehensive evidence base and route map. Where drug costs are particularly high, there may be opportunities for risk sharing and/or flexible pricing payment models to help mitigate against the risk and budget impact. It is also important to be aware that conditional marketing authorisations are often based on outcomes collected from real-world evidence, with information from registries required as standard practice to build on an initial evidence base.

Rob concluded with: “It is a challenge: but there is a lot of support out there and the momentum is going in the right way. What’s critical is to access and leverage support available to help get it right the first time so you’ve got a clear pathway. You need to understand what’s required and how you can work around anything that’s missing so that everything is working in a smooth process. Using the analogy, this will help you to capture the opportunities to climb the ladders and avoid the pitfalls of landing on a snake.”



It is a challenge: but there is a lot of support out there and the momentum is going in the right way.

Robert Whitmore
Founder/Owner – Roboleo & Co Ltd



For patients, one of the worst things is knowing a drug is there and works but they can’t access it.

Dr Melanie Lee, CBE. CEO – LifeArc

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N-acetyl-L-leucine (IB1001)

- ✓ Active neuroprotective enantiomer
- ✓ Superior clinical benefits when administered independently
- ✓ Symptomatic and disease-modifying treatment potential
- ✓ Well-established safety profile
- ✓ Potential clinical benefits when administered independently
- ✓ Formulated for target populations (orally administered sachet, gluten-free)



You need the partnership, insight and the collaboration with patient organisations to ensure rare–disease trials are ethically and scientifically appropriate, feasible to conduct and able to demonstrate a meaningful treatment effect.

Taylor Fields, Senior Vice President, IntraBio

Structure of the Ataxia telangiectasia and Rad3 related (ATR) protein, which is closely related to the Ataxia telangiectasia mutated (ATM) protein
©Ismail Jarmouni, Wikipedia

Repurposing a vertigo drug as a treatment for inherited neurodegenerative diseases

Taylor Fields, Senior Vice President of IntraBio, stressed the importance of faster development programmes, particularly for patients with progressive conditions where the window of therapeutic opportunity may be lost.



20

Neurological conditions that the medicine has been investigated in compassionate-use programmes since 2010

IntraBio is currently investigating the drug, N-acetyl-leucine, a chemically modified version of the amino acid leucine. The racemic compound, N-acetyl-DL-leucine, contains two 'mirror images' called enantiomers and gained marketing authorisation in France in 1957 as a treatment for acute vertigo.

Since 2010, the medicine has been investigated in more than 20 neurological conditions in compassionate-use programmes, which have provided evidence it can reduce symptoms and provides neuroprotective benefits. Some of the greatest effects are in children and adults affected with rare and devastating inherited progressive neurodegenerative conditions with high unmet needs including:

- **Niemann-Pick disease type C (NPC)** caused by a build-up of cholesterol and other fatty substances in the liver, brain and spleen.
- **GM2 Gangliosidosis (Tay-Sachs and Sandhoff disease)** mainly affecting babies and young children, this is a devastating condition that stops the nerves from working properly and is usually fatal.
- **Ataxia Telangiectasia (A-T)** a complex disorder that affects the nervous system, immune system and other body systems.

The company set up a 'reverse translational' approach – going back to the laboratory to understand more about the drug's mechanism of action in these indications.

These experiments revealed that the 'L-enantiomer', N-acetyl-L-leucine (IntraBio Code 'IB1001') is responsible for the long-term, disease-modifying effects and this enantiomer appears to have superior clinical effects when administered independently.

Clinical testing

IB1001 is currently being investigated in three separate, multinational, open-label, rater-blinded Phase II studies as a treatment for these rare neurodegenerative diseases.

Taylor highlighted that the existing compassionate use data helped to inform the clinical trial design and to establish clinically relevant outcomes. But there were also major challenges – including the potential for patients to source alternative unlicensed versions of the drug, which limited their ability to conduct a randomised, placebo-controlled study. It also proved difficult to define how best to measure the drug's effectiveness for such rare conditions that vary so widely in their heterogeneity of symptoms, as well as the severity of the disease and rate of progression between patients.

Taylor emphasised that working early and often with patient organisations is vital for overcoming these challenges. "You need the partnership, insight and the collaboration with patient organisations to ensure rare disease trials are ethically and scientifically appropriate, feasible to conduct and able to demonstrate a meaningful treatment effect," she advised.

Working in partnership

Drug repurposing for rare diseases is a rich and dynamic ecosystem involving many different stakeholders. But it is vital to make sure that the patient voice is at the heart of all opportunities.

Every drug repurposing opportunity is unique. While there is no set route for taking an existing medicine to patients with a rare disease, working collaboratively using a patient-centred approach provides the best chance of a successful outcome.

Academia is often the originator of a drug repurposing opportunity, but early partnering is key to support clinical trials - with different pathways for patented or generic products.

Patients and charities can also play a critical role in drug repurposing, with the initial push around an opportunity often coming from patients and patient advocacy groups. These groups are also key for helping accelerate clinical trials through outcome measures frameworks and outreach to patients to improve recruitment. They can also provide a source of critical real-world evidence (including quality of life measures) through disease-specific patient registries.

The payer is concerned about constrained healthcare budgets, which are coming under additional pressure from the increasing burden of obesity, chronic diseases and an ageing population, as well as the impact of the COVID-19 pandemic. Achieving the right balance between value for money and patient benefit often relies on competition between companies, but this model is more challenging for drug repurposing. Clinical trials offer a potential route for existing drugs to reach patients with rare diseases sooner without a cost to the payer.

Managing off-label use will also raise concerns for the healthcare provider and current manufacturer, including challenges with risk management and the effective use of products for different indications. Getting products licensed for the new indication is key for ensuring that repurposed drugs are made available to patients. Receiving an accurate diagnosis is also vital to ensure eligibility, which can sometimes take decades for patients with certain rare conditions.

Regulators are introducing accelerated approval processes that can help expedite drug repurposing opportunities. They can also provide advice on gathering the real-world evidence needed to support conditional marketing authorisation, which can prove challenging for rare diseases.

Finally, there is industry. There are multiple business models for rare diseases and repurposing - for both generics and patented products. There is also an increasing role for data aggregators to produce real-world evidence - and for artificial intelligence (AI) companies that can mine those rich datasets to identify potential repurposing opportunities.

Industry



Multiple business models for rare diseases and repurposing

Increasing role of data aggregators and artificial intelligence (AI) - to identify potential repurposing opportunities

Managing off-label use.

Payer



Constrained healthcare budgets

Need to balance value for money and patient benefit through competition

Need for short term cost benefits

Economic value of life sciences ecosystem

Patient groups and charities



Push for drug repurposing

Key to rapid clinical trials recruitment

Source of real-world evidence and direct and indirect health benefits

Healthcare provider



Reducing time to diagnosis

Managing off-label use

Clinical trials support

Regulator



Accelerated marketing authorisation processes and conditional marketing authorisation (CMA)

Limited patient data

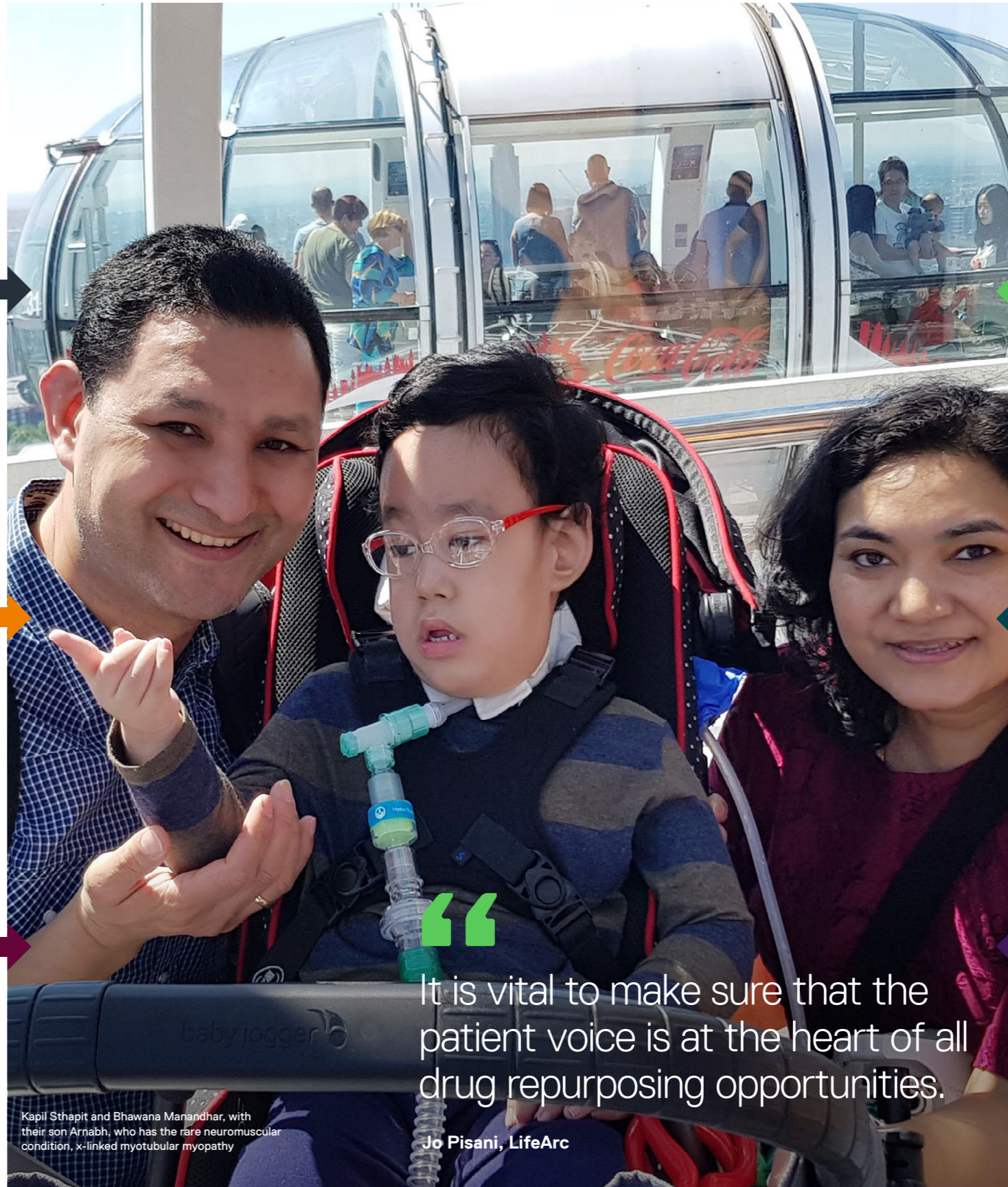
Real-world evidence to support CMA

Academia



Often originator of repurposing opportunity

Need early partnering for clinical trials



It is vital to make sure that the patient voice is at the heart of all drug repurposing opportunities.

Jo Pisani, LifeArc

Kapil Sthapit and Bhawana Manandhar, with their son Arnabh, who has the rare neuromuscular condition, x-linked myotubular myopathy

Drug repurposing: seizing the opportunities

Drug repurposing is a dynamic and innovative field with the potential for major benefits for patients. But translating the potential of the approach into clinical practice to improve outcomes for patients remains challenging.



Developing an entirely new medicine by traditional drug discovery is lengthy, time-consuming and expensive. Drug repurposing, which can be driven by a serendipitous discovery or data-driven strategies, is gaining momentum as an effective alternative approach. While the path to getting these existing medicines to patients is not straightforward, a range of different business models are beginning to emerge.

In 2017, the AMRC released the report, 'Facilitating the adoption of off-patent, repurposed medicines into NHS clinical practice.' NHS England and Improvement (NHSEI), in partnership with others, subsequently developed a report on how those national agencies would collect, address and action key repurposing opportunities.

These activities have led to the Repurposing Medicines Programme, which was launched in March 2021. This NHS England paper aims to identify and pursue opportunities to strengthen the evidence base, licensing, supply, cost-effectiveness and equitable adoption of currently unlicensed or off-label medicines, where there is a benefit to the NHS and patients.

"We will continue to support charities and academics as they navigate this rapidly evolving landscape, enabling more patients to reap the potentially life-changing benefits from existing medicines as soon as possible," says Melanie Lee, CEO of LifeArc.

Key success factors for drug repurposing:

- ✓ Involve patients every step of the way
- ✓ Work in partnership with different stakeholders
- ✓ Identify knowledge gaps and carry out necessary pre-clinical work
- ✓ Develop an IP strategy as early as possible
- ✓ Seek scientific advice from the MHRA
- ✓ Take steps to ensure drug accessibility early on



We will continue to support charities and academics as they navigate this rapidly evolving landscape, enabling more patients to reap the potentially life-changing benefits from existing medicines as soon as possible.

Dr Melanie Lee, CBE
CEO – LifeArc

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Taylor Fields Senior Vice President, IntraBio

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Cover image: Courtesy of the Myotubular Trust, Shutterstock

Further reading

Opportunities for Repurpose Medicines in the NHS in England (2021).

www.england.nhs.uk/wp-content/uploads/2021/03/B0342-opportunities-to-repurpose-medicines-in-the-nhs-in-england.pdf

Association of Medical Research Charities (AMRC) report (2017) - Facilitating adoption of off-patent, repurposed medicine into NHS clinical practice.

www.amrc.org.uk/Handlers/Download.ashx?IDMF=c1a3904c-78de-47ed-813c-b34b57ca587c

Findacure, Information on drug repurposing for rare diseases:

www.findacure.org.uk/drug-repurposing/

Saving and improving lives: the future of UK clinical research delivery (March 2021).

www.gov.uk/government/publications/the-future-of-uk-clinical-research-delivery/saving-and-improving-lives-the-future-of-uk-clinical-research-delivery

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