+ TRENDS IN ANTI-COUNTERFEITING

+ PHARMA AND THE SUPPLY CHAIN

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September/October 2021

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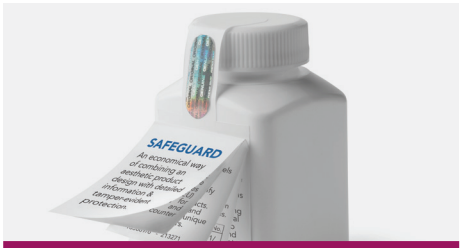

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PRACTICE MAKES PERFECT

As Winter looms here in the UK, once again we're hearing about a season of turmoil for the NHS and its patients.

With general practitioners acting as patients' first port of call, it should come as no surprise that the government is looking at what it can do to alleviate pressures over the coming months. As such, Sajid Javid, the UK's somewhat rather invisible health and social care secretary, has announced a £250 million package to help GPs boost capacity over the winter and provide more appointments to patients.

One of the caveats? GPs must provide clear plans on how they improve access and deliver more face-to-face appointments.

The reasoning behind Javid's plan is unclear. During the pandemic, face-to-face appointments in the UK dropped to below 60%, as many practices pivoted towards digital solutions such as telehealth and video conferencing technology to provide care to patients. But that doesn't mean the service provided to patients was poor - just that it was different. If anything, the adaptive nature of GPs throughout Covid-19 should be applauded rather than vilified.

The Royal College of General Practitioners words it better. They say that a focus "purely on access" ignores the other challenges doctors face in providing "high-quality, personalised care."

Personalised care should be the key phrase in this regard. In a time when the digital health industry is continuing to grow, surely it makes sense to utilise the technology we have available in order to provide digital and remote care to patients. Of course, those wanting to attend a practice in person should be able to do so and digital appointments can only help bolster this availability.

It feels as if Javid's plan is nothing more than a sticking plaster for a service that has been bleeding from a lack of staff for years now. Former health secretary Jeremy Hunt knows too well the sector in which Javid now operates. Even he took to social media to call out the government's plan as nothing more than a temporary fix.

That the former health secretary and the RCGP agree on what is needed to help GPs should be taken seriously by Javid. They're both calling for a long-term solution to the staffing problem the sector has faced for years now.

The government needs to stop thinking in reactionary terms and focus on hitting its manifesto pledge of an additional 6,000 GPs by 2025. Crucially, Javid needs to understand that quality of care is not always dictated by its format. The option for GPs to hire locums may help alleviate some of the pressures over the winter but as a long-term solution it simply won't do.

EDITOR'S DESK

PsyProtix launches to develop therapies for treatment-resistant depression

Biopharmaceutical company atai Life Sciences and Duke University biotechnology spinout Chymia have teamed up to launch a platform company aiming to transform the treatment of mental health disorders.

PsyProtix will be a precision psychiatry company focused on developing therapeutics for treatment-resistant depression (TRD) and other mental health indications.

PsyProtix will apply precision psychiatry approaches to treat mental health disorders by factoring each patient's variability in genes, metabolism, environment, and lifestyle. A newly emerging field, precision psychiatry is designed to allow physicians to prescribe treatments specifically targeting an individual, rather than testing out which treatments such as antidepressants work best.

"Our view is that each patient is unique, meaning that any given patient will likely have specific individual needs," said Srinivas Rao, chief scientific officer and co-founder of atai Life Sciences. "This emerging technology adapts to the variability of conditions, such as depression, with the aim of allowing patients with psychiatric disorders to potentially be diagnosed and treated more accurately and efficiently according to their specific needs. It's an honour to be collaborating with professor Rima Kaddurah-Daouk and her team at Duke, given their great work in advancing the research of metabolomics and their study of neuropsychiatric disorders."

Depression is the leading cause of disability worldwide, according to the World Health Organisation (WHO) and is thought to affect over 264 million people worldwide. Whilst the prevalence of patients with treatment-resistant depression varies in estimation, a study published in 2021 in the Psychiatrist estimated that out of 8.9 million people in the US being treated for major depressive disorder (MDD) 2.8 million had TRD.

HIKMA TO ACQUIRE CUSTOPHARM IN $375M DEAL

Pharmaceutical company Hikma has acquired Custopharm in a deal initially worth $375 million.

Hikma, a supplier of generic injectable medicines in the US will pay a further $50 million if certain commercial milestones are met.

Custopharm is a US-based generic sterile injectables company with a differentiated product portfolio and R&D pipeline. It currently markets its products in the US through its commercial arm Leucadia Pharmaceuticals. In 2015, it partnered with Water Street Healthcare Partners and has since received 13 US FDA approvals.

Siggi Olafsson, chief executive officer of Hikma, said: "This acquisition provides Hikma with an attractive opportunity to further strengthen our US injectables business, by adding an attractive and profitable portfolio of marketed products and an exciting pipeline of future opportunities. Custopharm is an accomplished operator in the US injectables market with a first-class scientific team and a strong regulatory track record. This acquisition is highly complementary to our existing business and adds high-quality and differentiated growth potential."

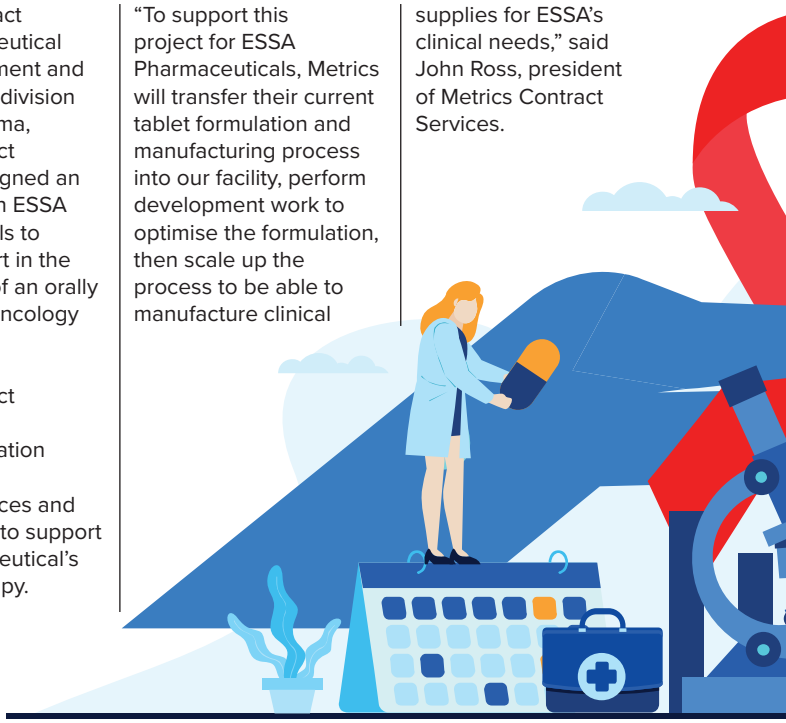
William C. Larkins, CEO of Custopharm and Leucadia, added: "We're

Metrics to provide support to ESSA's oncology drug

The contract pharmaceutical development and manufacturing division of Mayne Pharma, Metrics Contract Services has signed an agreement with ESSA Pharmaceuticals to provide support in the development of an orally administered oncology drug.

Metrics Contract Services will provide formulation development, analytical services and manufacturing to support ESSA Pharmaceutical's oncology therapy.

"To support this project for ESSA Pharmaceuticals, Metrics will transfer their current tablet formulation and manufacturing process into our facility, perform development work to optimise the formulation, then scale up the process to be able to manufacture clinical supplies for ESSA's clinical needs," said John Ross, president of Metrics Contract Services.



excited to become part of Hikma, a global leader that shares our deep commitment to bringing generic products to market and into the hands of patients who need them. Water Street has been an outstanding partner in working with us to build an exemplary portfolio of complex generic products. We're looking forward to building on this success."

The project will enable Metrics to demonstrate not only its long-time expertise in supporting customers with development programs and its unique ability to support commercial production from the same campus, but also its leadership in producing novel oral solid dose therapies for oncology treatment.

"We are excited to partner with ESSA on a programme that is ultimately intended to benefit cancer patients. Our focus is keenly on novel drugs that make a difference," Ross added.

MOONLAKE IMMUNOTHERAPEUTICS AND HELIX COMBINES TO CREATE NEW BIOTECH

Clinical-stage biotechnology company MoonLake Immunotherapeutics and Helix Acquisition Corp, a special purpose acquisition company, have agreed to combine their businesses to create a new immunology company.

The combined businesses will be named MoonLake Immunotherapeutics and its stock is expected to be listed on Nasdaq under MLTX.

In addition to the approximately $115 million held by Helix Acquisition Corp, the transaction also includes commitments for a $115 million private investment in public equity (PIPE).

Proceeds from the transaction are expected to provide MoonLake with the capital needed to accelerate the development of the clinical stage, tri-specific Nanobody sonelokimab, in multiple inflammatory diseases in dermatology and rheumatology. So far, sonelokimab has been tested in a Phase 2b trial with over 300 moderate-to-severe psoriasis patients.

MoonLake now plans to initiate additional Phase 2 studies targeting other IL-17A/F driven indications such as psoriatic arthritis (PsA), ankylosing spondylitis or radiographic axial spondyloarthritis (AS or RaxSpA), and hidradenitis suppurativa (HS), each of which affect millions of patients worldwide.

Jorge Santos da Silva, CEO of MoonLake said: "This financing is an important milestone for our company. On behalf of the founders, we are grateful to the MoonLake team and our investors for ensuring access to the capital we need to advance our sonelokimab clinical programs, and create the potential to transform the lives of patients affected by IL-17A/F-driven inflammatory diseases. We would like to congratulate Cormorant, all of our investors, and the MoonLake team for their contributions to reaching this important stage, and we look forward to our immediate next steps, including the imminent start of our innovative Phase 2 program."

Bihua Chen, founder and CEO of Cormorant, and CEO of Helix said: "MoonLake has a strong management team with deep scientific and operational experience in immunology and an exciting asset in sonelokimab, which has already shown clinical benefit in psoriasis. We are excited about the potential for sonelokimab impacting diseases such as HS, PsA, and AS or RaxSpA."

PERSPECTIVE ON PHARMA:

One biotech's mission to change the standard of cancer care

At some point during a cancer patient's treatment pathway there can come a trade-off between the desired level of drug they're taking and just how well they tolerate the side-effects that inevitably come with treatment.

For people with cancer, the choice between extending their lives on a drug that will cause extremely unpleasant side-effects, versus forgoing treatment for a better remaining quality of life, is obviously a tough one.

Pedro Lichtinger has worked in the pharma industry for most of his professional life, leading Pfizer's global primary care business and managing two biotechs in his time. Four years ago, he and colleagues launched Starton Therapeutics, an oncology-focused start-up that is looking towards transdermal delivery as a means of treatment for cancer patients.

"We believe in our focus in using our technology to transform outcomes for patients. Basically, improving efficacy and the tolerability of drugs [in cancer care]," Lichtinger says.

Whilst transdermal patches aren't a new technology, their use, as Lichtinger tells me, has primarily been used as a means for convenience, rather than for any clinical benefit.

"Transdermal patches don't offer a true clinical benefit, they offer non-inferiority to the original molecule but they're more convenient to the patient and hopefully they improve compliance," Lichtinger says. In cancer care that model doesn't work. "Payers are not willing to pay for convenience. Therefore, there are very few transdermal patches that have

Pedro Lichtinger, CEO and chairman of biotech Starton Therapeutics speaks to EPM about the company's mission to improve cancer care using transdermal technology.

significantly impacted patients, he adds."

This is something that Starton wants to change. The company has developed a transdermal delivery system for approved drugs in a bid to increase their efficacy and make them more tolerable for patients so that they can receive continuous treatment. The company has several products in both pre-clinical and clinical stages but perhaps most interesting is its project involving a blockbuster cancer drug and a new indication for it.

Revlimid is one of the highest selling drugs in the world. It is an immunomodulatory drug (IMiD) used as a standard of care therapy for people with multiple myeloma. Through its STAR-LLD project, Starton is taking Revlimid and turning it into a therapy that can be taken via a skin patch. The indication? Chronic lymphocytic leukaemia (CLL), the most common form of leukaemia in adults.

Whilst Revlimid is one of the most successful drugs in the world, its method of delivery brings with it many of the issues that are found in other oncology treatments – those of efficacy, tolerability, and resistance.

"Revlimid has a three-hour half-life and it's taken every 24 hours. We know by modelling that at 12 hours you fall below the minimum efficacious level and at 14 hours you start having no detectable levels in the cancer patient. What that means is you are giving, every single day, the cancer cells the opportunity to create resistance and to recover from the attack of the medicine."

Starton wants to avoid this by delivering Revlimid in a continuous manner through its transdermal technology. Specifically, the treatment would consist of a low dose of Revlimid, delivered continuously so that patients always have an efficacious level of drug in their system.

One of the biggest impacts of cancer on both the patient and their friends and families is just how seriously the adverse effects of treatments can be.

"When you look at the average, treatments [for cancer] extend life relatively shortly – 18 months, three years," Lichtinger says. "After that they really start to impact quality of life. We all have members of our families or friends that have gone through cancer and their treatment can make them miserable. They are sick, they're nauseous, they have infections – it's very sad, that quality of life."

However, pivoting to a continuous delivery method could reduce the high levels of a Revlimid found in a patient's plasma, helping to improve tolerability and therefore, improving a patient's quality of life.

In a drug like Revlimid, which sees many patients opting to reduce their dosage due to its side-effects, this is crucial.

"What people don't realise is that when you go from 25mg to 15mg, you reduce the period of extended life for that patient. That's the story of a very large number of drugs where doses are reduced because patients cannot tolerate it," Lichtinger says.

Starton hopes that if people can tolerate Revlimid in a continuous dose, then CLL could become akin to something like a chronic disease, increasing a person's lifespan and offering them a healthy quality of life.

Of course, as it stands, this is all theoretical, but Lichtinger is encouraged by proof-of-concept studies in mice which showed that continuous infusion of Revlimid displayed superior efficacy to a standard of care approach.

Starton's journey so far has been somewhat different to other biotechs. The company opted not to raise funding through traditional means such as venture capital firms and instead has a cohort of 250 individual investors. This year, the company became one of the first biotechs to raise funding through the reality investing show, Unicorn Hunters, on Amazon Prime.

> "What people don't realise is that when you go from 25mg to 15mg, you reduce the period of extended life for that patient.

Lichtinger himself pitched Starton before the show's judges, asking for between $20-30 million to further develop the company's transdermal technology and progress towards clinical studies. Two of the judges took Lichtinger up on his offer and now he believes Starton is in a good position to expand its operations before it plans on making an initial public offering (IPO) in the coming months.

But, despite the novelty of Starton's journey, Lichtinger is adamant that he wants Starton to be a biotech that caters to patients by avoiding high pricing (as seen in the US with Revlimid) and by increasing its access across the globe.

"Part of our strategy is to work with different regions and countries to make this available to patients. We are not going to follow the traditional model of very high pricing, focused only on the US. We want to make this available to many countries and are developing a strategy for access that will allow that," Lichtinger says.

> Inclusion needs to be in the design process, not just to avoid inconvenience but to avoid serious consequences for the public.

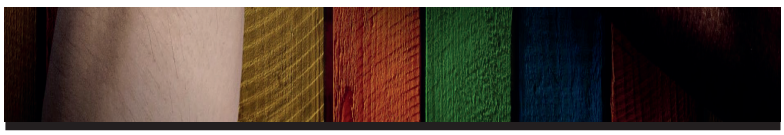
HOW INCLUSION AFFECTS PRODUCT DESIGN IN PHARMA

Author:
RAAFI-KARIM ALIDINA, consultant at Included

Many organisations are realising the need for change. This has been catalysed by the Black Lives Matter movement and the inequalities highlighted by the pandemic. The need to be actively anti-racist has become more apparent and urgent, with organisations rightly under pressure from internal and external forces. This leaves leaders with the task of addressing bias in processes, structures, and behaviours. Many turned to technology, on the logic that this would remove the bias that is unconscious in people and create a more equal, inclusive approach. This thinking, however, is flawed as these machines and algorithms are still created by people. This leads to the creation of biased technology.

BIAS IN TECHNOLOGY DESIGN

Recently, I went to a barbecue restaurant with my partner. When I went to the bathroom to wash my hands, everything was touchless: there were automatic faucets, hand dryers, soap dispensers, even an automatic paper towel dispenser. However, as soon as I tried to use any of them, they wouldn't work! No matter what I did, I just couldn't get the sensor to detect my hands and dispense water or soap. Then, someone else came into the bathroom and tried to wash his hands and everything worked perfectly. What was the difference? His skin was white, while mine was brown. If you're a person of colour, you're probably familiar with the fact that many automatic dispensers in public bathrooms don't work as well for you as they do for your white friends.



This stems from how these products were designed and who they were designed by. They were built on a training set that was not diverse, using pictures of predominantly white skinned hands, thus embedding this bias into how the product would function. When it impacts automatic taps, hand dryers, and soap dispensers it is an annoying problem for people of colour. But the real problem comes when the same object-detection system is deployed in technology such as self-driving cars. A study at Georgia Tech University in the US found that many of the autonomous vehicles being developed that used these systems were significantly worse at detecting – and so stopping for – dark-skinned pedestrians. This technology could pose a very real threat to Black and brown people and lead to injuries and deaths. This isn't the only example of coded bias and it impacts all kinds of products. From crash test dummies that are modelled exclusively on the average male body, Amazon's biased hiring algorithm, to Google's failed launch of their reverse image search (which identified Black people as 'gorillas'), or even a lot of voice recognition software that can't accurately detect the voices of Black people.

Inclusion needs to be in the design process, not just to avoid inconvenience but to avoid serious consequences for the public.

Two main issues drive this coded bias. Firstly, the lack of diversity in the product building teams. Non-diverse teams are less likely to spot issues that may impact a different demographic group than those they are part of. Secondly, there is a lack of inclusion in these teams. Where diverse teams exist, those from marginalised groups are often not able to speak up and be heard. This can be due to insufficient psychological safety stemming from the organisation's culture.

HOW DOES THIS IMPACT PHARMA?

Pharma is not immune to this coded bias. For example, women have been excluded from drug trials for decades with no evidence-based justification for not including a demographic that makes up 51% of the global population. This has very real implications, as the dosage amounts have been decided by male-dominated clinical trials which has led to women experiencing worse side effects than their male counterparts. For example, a recent study from UC Berkeley and UChicago conducted in 2020 found that across the 86 drugs they looked at, women suffered worse side-effects in over 90% of cases. These side effects were not just headaches and nausea, but major issues like seizures, hallucinations, and cardiac anomalies.

The study notes that even extremely common drugs like Ambien have different effects on men and women – it "lingers longer in the blood of women than of men, causing next-morning drowsiness, substantial cognitive impairment, and increased traffic accidents." It wasn't until 2013 that people noticed and dosage recommendations decreased for women.

As with the coded bias in technology, a lack of team diversity and inclusivity is the driving issue here. Teams made up of people from a similar background are more likely to have a blind spot and less likely to notice that a clinical trial group isn't representative of the population. Teams that are diverse and representative still must ensure an environment of psychological safety is created in order for team members from non-dominant groups to be able to speak up and be heard if they notice a bias, blindspot or mistake.

WHAT IS THE SOLUTION?

There must be a conscious and deliberate decision to embed inclusion and diversity in the process that is used when designing new products. This includes medications, medical devices, and all treatment methods. By taking this approach, pharma companies can minimise the risk of default biases being reflected in the final product created.

Some ways in which this can be realised are through adding an:

- Inclusion review. Bringing this into the product development process, similar to a legal review, acts as a check to ensure any blind spots are covered.
- Inclusion checks at different points of the process. This leverages the insight of a diverse team at specified checkpoints throughout the product design and development process. Teams can actively engage their members, asking everyone to specifically comment on any potential bias that they can identify in the way the research is being conducted.
- Start and end the product lifecycle by reflecting on your identities and biases. This provides an opportunity to question and engage with one's own biases and those of the team as a whole. This means the product team can begin the project with an inclusive mindset before beginning development. By including this at the project's conclusion, a retrospective learning opportunity is present to allow for a culture of continuous improvement to drive future design.

These steps can help pharma and all industries create more inclusive products. Each solution is active, as passive solutions will not help create the better world we are seeking to build. To stop making avoidable mistakes that risk harming people, active steps need to be taken by each of us to embed an inclusive approach to the way we do our work each day.

Pharma industry warned not to undo advances made during pandemic

The president of global not-for-profit, The Pistoia Alliance, Dr Steve Arlington is calling on the pharmaceutical industry to continue to build on the advances it has made during the Covid-19 pandemic.

Dr Arlington states that the industry should continue to place its focus on the types of collaborative efforts that we've seen during the past two years. In particular, companies should be wary of returning to old ways of working which could slow down progress.

Digital transformation has accelerated rapidly during the pandemic, which in turn has greatly improved remote patient monitoring, rapid online triage of patients, and the sharing of data.

"While we have made incredible scientific gains to address Covid-19, there are still many disease areas where very little has progressed in the last four decades, in terms of both treatments and outcomes for patient," Dr Arlington said.

To address the numerous public health issues facing society, The Pistoia Alliance believes that global solutions developed through collaboration are required. This should involve stakeholders in governments, regulatory authorities, and the biopharmaceutical sector, who must all take a cross-disciplinary approach if they are to solve issues such as real-world patient data for use in R&D.

"The biopharmaceutical sector has done a lot during the pandemic to rebuild trust in the industry. It now needs to take that even further to educate the public on the importance of data sharing, including the benefits of sharing their anonymised patient data. Many people have been understandably concerned about sharing personal information, but to enable big breakthroughs in areas like cancer and precision medicine, we all need to altruistically share our data for the greater good of research," Dr Arlington added.

Did you know?

There are 21 vaccines in use for Covid-19.

There are 333 treatments for Covid-19.

The first Covid-19 vaccine was authorised for emergency use in just 11 months.

MEDICINES DISCOVERY CATAPULT SCIENTIST WINS EARLY CAREER IMPACT AWARD 2021

Dr Laura Ajram, Psychiatry Consortium programme manager at Medicines Discovery Catapult (MDC) has landed the ELRIG Early Career Impact Award 2021 for her work.

The award, given by the European Laboratory Research and Innovation Group (ELRIG) recognises and celebrates the achievements of early-career professionals (ECP) who have made a clear, demonstrable impact on the wider scientific community.

Dr Ajram was awarded the accolade for her work in the inception and management of MDC's Psychiatry Consortium; a collaboration between medical charities, pharma and healthcare organisations, focusing on novel drug discovery in mental health.

Dr Laura Ajram, Psychiatry Consortium programme manager at MDC, said: "I am driven by a desire to bring people together in collaboration to offer different perspectives and make research even stronger. Through the Psychiatry Consortium, we are seeing the benefits of this approach. It is great that ELRIG acknowledge all the roles that play a part in delivering exciting science, and I hope that by winning this award I inspire others to actively engage in meaningful research collaborations that could lead to the drug discovery breakthroughs of tomorrow."

GONE IN A *FLASH*

The journey SPI Pharma made into developing a game changing patient-centric drug delivery platform.

For pharmaceutical manufacturers, some of the most important considerations when it comes to developing medicines is how patients are going to respond to the physical act of taking them. If it's a tablet, what does it taste like? Could there be swallowability issues? Is it dissolvable?

This last question is an area in which ingredients supplier, SPI Pharma, specialises in. When it comes to oral dose products like tablets, the effective delivery of those drugs is key if patients are going to comply with their treatment regime.

This idea of patient centricity is what brought SPI Pharma to develop its latest excipient platform –UltraBurst - for orally dispersible tablets (ODTs).

SPI Pharma started developing UltraBurst in the middle of 2020. The company looked at its original platforms for ODTs and found that it could improve upon that technology with a rapid disintegration "flash" platform. In other words, it could take traditional ODT formulations and aim to make them dissolve in under 10 seconds – what SPI Pharma classes as "flash" disintegration.

"The innovation in UltraBurst is that it takes the current excipient platform and moves the disintegration time to a faster range than what's currently on the market," Bill McCarthy, global marketing manager of excipients and drug delivery systems, SPI Pharma told EPM.

Article and interviews by EPM editor **Reece Armstrong.**

What this means is that 50-200mg tablets can see disintegration times range from four to nine seconds compared to the usual 12-15 seconds. For larger tablets of 500mg, UltraBurst can help reduce disintegration time from 80-90 seconds with conventional platforms, to just 12 seconds.

For formulators, the three most important characteristics of ODTs are disintegration time, tablet robustness and organoleptic properties – or the feel of a tablet in the mouth. McCarthy explains that whilst there are several ODT excipient platforms available on the market, those that are able to provide "flash" disintegration are very expensive and are limited to just a few suppliers.

"What we saw was an opportunity to create an excipient preformulation that could keep tablet robustness and good mouthfeel, but enable faster disintegration time," McCarthy says.

McCarthy tells me that SPI Pharma often works with its customers to improve their formulations and that the company had developed

several examples of Flash ODTs to demonstrate their expertise and range of capabilities in the space. After their customers saw the examples they had been working on, and showed continued interest, SPI Pharma knew that they had a product that would be welcomed onto the market.

The development of UltraBurst makes sense for a company that has been in the orally dispersible dose market for decades.

"It's where we play," McCarthy says. "One of our major product groups - mannitol excipients - is widely used in these types of dose forms. We also have a major business selling antacid actives for chewable and meltaway tablets, and we launched the first directly compressible, ODT excipient platform- Pharmaburst, in 2003."

Perhaps more importantly however, is the role these types of dosage forms play in improving medicines, helping to increase compliance, resulting in better efficacy. Simply put, patients prefer tablets that dissolve immediately. Faster disintegration results in a better experience for a patient and makes it a more appealing product than one that takes longer to dissolve. More so, the patient friendly nature of an ODT means that for anyone with difficulty swallowing, it can be their preferred dosage form.

It isn't simply a better patient experience that it offers though.

"Very rapid disintegration also creates possibilities for designing formulations with enhanced oral mucosa or sublingual uptake of the drug - which could open possibilities for formulations with enhanced bioavailability," McCarthy explains.

And whilst this isn't something SPI Pharma has validated with UltraBurst, the company is currently exploring those types of formulations.

Of course, making drug delivery more patient focused is a welcome effort but only if the formulations that are being produced through UltraBurst are able to retain their API (active pharmaceutical ingredient) stability.

"Achieving content uniformity for low dose micronized actives requires understanding of the API characteristics and how these interact with the excipient platform," McCarthy says.

"Larger tablets and tablets with higher drug loadings can be challenging since achieving faster disintegration times becomes more difficult as the tablet size increases or API properties mask the functionality of the excipient platform. Fortunately, UltraBurst is designed to overcome these challenges as it relies on multiple mechanisms to promote tablet disintegration."

In a time when manufacturing costs can form a significant part of a developer's overall costs, the need for affordable processes is evident. SPI Pharma has designed UltraBurst to support low manufacturing costs through direct compression manufacturing – a method which removes the need for granulation by having tablets compressed directly from their powdered active drug substance and the excipients.

Developing and launching a product in the midst of a global pandemic was certainly a challenge for SPI Pharma. "We had to adjust to digital just like everyone. This was particularly challenging as we have development labs in India and the production facility in Michigan, USA," McCarthy says.

"Tech transfer and scale up usually would have some element of in-person collaboration. We had to manage without that. Luckily, we have developed a robust new product development process and running that process was the key, even if it had to be done virtually."

**UltraBurst and Pharmaburst are trademarks of SPI Pharma*

"We had to adjust to digital just like everyone. This was particularly challenging as we have development labs in India and the production facility is in Michigan, USA.

The role logistics plays in pharma's journey into the future.

DELIVERING THE FUTURE OF PHARMA

Author: NIELS VAN NAMEN - executive vice president, Healthcare at CEVA Logistics

Author: STEPHEN BARKSFIELD - global BD program director, Healthcare at CEVA Logistics

The pace of change across the pharmaceutical industry is growing at an ever-increasing rate. Over the last decade, demand from global markets has challenged the industry to act more quickly to produce much needed innovative treatments. With the aid of technology over the past decade, the industry has fundamentally changed the way it operates.

Today, changing molecular and technology shifts are driving new research methods. Small molecule drugs, many of which date back to the 1800s like aspirin that is composed of just 21 atoms, now compare with a growth hormone drug of around 3,000 atoms or a large biologic drug of 25,000 atoms. Accordingly, the complexities of production and distribution have grown in recent years.

BIOTECH GROWING SIGNIFICANTLY IN GLOBAL MARKETS

According to industry reports, biotechnology products are estimated to account for 35% of the overall market by 2026 with more diverse product types and therapies—many with shorter life cycles—leading the way. New ways of assessing, approving and monitoring medicines, combined with personalised treatments, have resulted in new modes of delivering healthcare, and this trend will continue to accelerate in the coming years.

In general, these biologics are more susceptible to impurities in the production process and damage during transportation than traditional chemical entities. Gene and tissue-based therapies are especially difficult to manage, because with some treatments, samples must be individually extracted, propagated, prepared and tested before being administered. This requires a unique manufacturing set up and a logistics operation that is fully traceable for the individual patient.

HUGE SCOPE OF TRIALS DELIVERS EXTENSIVE, ONGOING PIPELINE

According to the US National Library of Medicine, more than 1,000 clinical trials are underway globally, representing a large pipeline for these products. Almost any gene in the human genome can be targeted, so the potential for new therapies is immense. Gene addition, gene correction, gene silencing, reprogramming and cell elimination are the five main therapeutic strategies in view. Other therapies, such as CART T-cell, have huge market potential with the hematological malignancy market alone expected to reach almost $4 billion by 2027, say industry observers, who also note that nearly 200 clinical trials for chimeric antigen receptor (CAR-T) cell therapies are in progress within just the G7 countries, and up to 100 other companies are working on a CAR-T therapy. This trend means these companies will require logistics support across their activities. In addition, the larger molecules mean greater product sensitivity, and therefore, greater expertise is required in their handling.

These changes will continue, and the future is all about embracing them. Koen Kas is a healthcare futurist, author and guest professor of molecular oncology and health tech at the University of Ghent in Belgium. He highlighted several stark examples during this year's CEVA Digital Live healthcare event. He pointed out that diabetes patients no longer have to take injections but can receive a small implant that delivers the needed drugs over six months. He also referenced tumor patients that can send their own cells to be modified and made stronger and have them returned to them. His point was that it's actually part of the patient that is starting to be transported.

MARKET TRENDS WILL DRIVE SUPPLY CHAIN REINVENTION TOWARD PATIENT CENTRICITY

In general, pharmaceutical production reflects the broader trends in healthcare. Changing demographics, ageing populations, global healthcare budget pressures and the move to home care combine to require an ever-closer relationship between producers, logistics providers and end-user patients. This relationship then merges with the changing nature of therapies and products, triggering more direct-to-patient services and home delivery of medication and diagnostics.

These new, targeted therapies present their own challenges, with affordability and accessibility being at the top of the list. Patients themselves are demanding a premium customer experience with telehealth and eCommerce driving changes in their behaviour. To this end, eCommerce health marketplaces are now creating new buying experiences for lifesaving, life-enabling medicines.

TRADITIONAL SUPPLY CHAINS MUST CHANGE TO MEET MODERN DEMANDS

Two decades ago, direct to patient was unheard of as a concept. A traditional pharma supply chain consisted of manufacturing the drug, transporting it to the wholesaler or distributor, delivering it to a hospital or pharmacy and then finally dispensing it to the patient. Patients had direct access to small quantities of over-the-counter drugs, but nothing more. For anything more complex, they went to a hospital, a doctor, or a pharmacy.

Today, that has all changed, with patient-centric fulfilment supply chains delivering strictly controlled, monitored, transparent and regulated interaction between all parties. Biotech and pharma have, like every other industry, been transformed by digital technologies and the use of predictive analytics, Big Data and AI-based tools, all of which give the industry the capacity to redesign its development, manufacturing and overall business processes.

Gene therapy and cell therapy, which are often combined to treat genetic diseases, are good examples of new treatments where expert partners need to work together in close cooperation to achieve the desired, individualised treatments. Oral formulations of large molecule drugs are difficult to produce, and as a result, many of these treatments need novel delivery devices that require dedicated handling and transportation. A large proportion of companies working on these therapies are small or mid-size enterprises requiring support from a logistics provider to create transport solutions for their therapies, especially at the scale-up phase of the development lifecycle in support of operations.

CHALLENGES – DRUG SAFETY

Looking at the current state of the industry, a number of challenges remain to be addressed. According to various industry associations and institutes, a pharma manufacturer can expect a damage rate of up to 30% attributable to the logistics constraints associated with its product. Some 25% of vaccines reach their destination degraded due to incorrect shipping, while 20% of temperature-sensitive products experience broken cold chains.

The only way to overcome these challenges and improve delivery outcomes—and therefore patient outcomes—is to use expert providers who can seamlessly deliver across the supply chain in all areas of biotechnology, as the culture and demands in the healthcare supply chain can vary significantly when compared with traditional supply chains.

LOGISTICS: DELIVERING END-TO-END ACROSS THE SUPPLY CHAIN

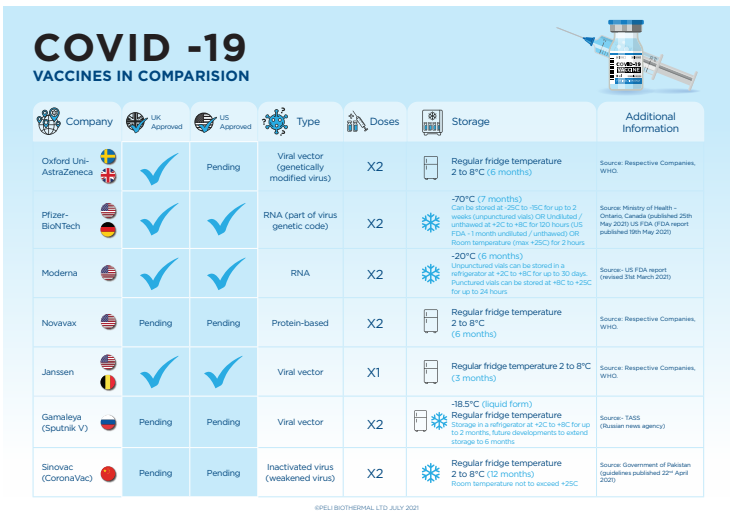
The shipment of pharma products demands a relentless focus on risk mitigation, continuous improvement, quality, service and regulatory expertise—in other words, ethical and operational excellence from one end of the supply chain to the other. The ultimate goal of healthcare logistics is to make healthcare accessible and affordable globally through seamless supply chain solutions.

> **In general, pharmaceutical production reflects the broader trends in healthcare.**

PROTECTING *the payload*

A summary of the temperature requirements needed to transport, store and use Covid-19 vaccines.

Author: ADAM TETZ - director of Worldwide Marketing at Peli Biothermal



When the first Covid-19 cases were reported, no one could have predicted the devastating impact this virus would wreak worldwide.

Developing Covid vaccines was the first step in the fight back against the virus. The world then faced the significant challenges of having to protect, transport and safely store temperature sensitive pandemic payloads worldwide.

Developing effective Covid-19 vaccines is only part of the battle in the ongoing fight against the virus. It's imperative the cold chain is maintained during shipping and storage, ensuring approved vaccines can be deployed worldwide without affecting the efficacy of any life-saving jabs.

It had been anticipated that the first year of the international inoculation programme would be dominated by the need globally for a complex, costly infrastructure, including vast freezer farms providing storage at temperatures of -80C.

However this has not been the case as temperature requirements have changed according to the rising range of vaccines being developed, approved and administered.

Collaborations with pharmaceutical companies, the Food and Drug Administration (FDA) and European Medicines Agency (EMA) resulted in the approval of the transportation and storage of vaccines at more manageable temperatures, including -20C and 2C – 8C.

The advantage of the introduction of vaccines which can be stored in a standard refrigerator at 2-8 degrees Celsius makes them more useful and accessible to developing countries, which may not be able to store large amounts of vaccine at low temperatures.

Although some vaccines still need extreme temperature requirements, which are more difficult and costly to maintain, requiring more exotic coolants such as dry ice to achieve -80C, what we continue to see are the various vaccines' tight temperature shipping and storage requirements changing at a rapid rate.

Temperature conditions are determined by the requirement of the vaccine or therapeutic that's developed and subsequently approved. We are now seeing the introduction of vaccines requiring more easily controlled temperatures during transit, storage and inoculation including -20C or +5C.

These temperature requirements can be maintained via the existing infrastructure of refrigerators and freezers, which are already in place at clinics and hospitals. It also aids the ongoing deployment of vaccines to more remote regions which are harder to reach or do not have the necessary infrastructure in place to transport and store vaccines requiring extreme temperature protection.

To meet the stringent temperature requirements for vaccine distribution from manufacturer to clinics, hospitals or pop-up vaccination centres, specialised thermal packaging products have been adapted and produced within the industry that are designed to protect and perform for every step of these vaccine journeys.

The temperature requirements for shipping and storage can be complex and as additional approved vaccines are produced, the logistics of transporting temperature sensitive pandemic payloads plays a major part in ensuring the worldwide vaccination programme remains on track.

VACCINES PROVIDING PANDEMIC PROTECTION

Although the shipping and storage requirements of emerging temperature sensitive vaccines vary, they all need protection to mitigate potential temperature excursions during transportation.

So how do the current approved vaccines compare when it comes to temperature transportation and storage requirements?

- **Pfizer/BioNTech** – The first Covid-19 vaccine approved for use in the UK and US, this RNA vaccine incorporates part of the virus genetic code and is administered in two doses.

  It can be stored at -70C for seven months.
  It can be stored at -25C to -15C for up to two weeks (unpunctured vials) or undiluted/unthawed at +2C to +8 for 120 hours (US FDA – one month undiluted/unthawed) or room temperature (max +25C) for two hours.

- **Moderna** - Also approved for use in the UK and US, this RNA vaccine is also administered in two doses. Can be stored at – 20C for six months. Unpunctured vials can be stored in a refrigerator at +2C to +8C for up to 30 days. Punctured vials can be stored at +8C to +25C for up to 24 hours.

- **Oxford/AstraZeneca** – Currently approved for use in the UK, Europe and being administered in numerous countries worldwide. This viral vector vaccine (genetically modified virus) is administered in two doses. Can be stored at regular fridge temperature of 2C to 8C for six months. Temperature requirements make it more manageable to ship to more remote regions.

- **Janssen** – Approved for use in the UK and US this viral vector single dose vaccine can be stored at a regular fridge temperature of 2C to 8C for three months.

- **Novavax** – Awaiting approval for use in the UK and US this protein-based vaccine requires two doses and can be stored at regular fridge temperature of 2C to 8C for six months.

- **Gamaleya (Sputnik V)** – This viral vector vaccine is currently being administered in Russia from where it originates, with Slovakia and Hungary also administering the two dose vaccine. Can be stored at -18.5C (liquid form) and storage in a refrigerator at +2 to +8C for up to two months, with ongoing developments to extend storage to six months.

- **Sinovac (CoronaVac)** – China's inactivated virus vaccine is currently being administered in several countries including Chile, Brazil, Indonesia, Mexico, Thailand and Turkey as well as China. It is the second Chinese vaccine (after the Sinopharm jab) to recently be granted approval for emergency use by the WHO. The vaccine can be stored at regular fridge temperature of 2C to 8C for 12 months and at room temperature not to exceed +25.

- **Sinopharm** – This two dose inactivated virus vaccine has a temperature storage requirement of 2C to 8C.

- **Covaxin (Bharat Biotech)** – Another inactivated virus vaccine administered in two doses with a storage requirement of 2C to 8C.

> **The advantage of the introduction of vaccines which can be stored in a standard refrigerator at 2-8 degrees Celsius makes them more useful and accessible to developing countries.**

The operational and financial impact of having access to real-time data and analytics across the pharma supply chain.

SEE SOMETHING, *SAY* SOMETHING... *DO* SOMETHING

Author:
SCOTT WHYTE - chief digital officer at AeroSafe Global.

Control towers in the traditional sense are integral to safe air travel. Operators are stationed in tall structures for 360-degree visibility of air traffic, along with radar technologies to augment what can be seen visually, and radio communications to relay vital updates to pilots. It's safe to say that most travelers and crew members would not fly without support from air traffic personnel sitting in the tower.

While biopharmaceutical supply chain control towers lack the soaring height of their air traffic counterparts, they offer visibility to ensure that prescribed medications arrive at their destination safely – particularly those that are temperature controlled. Today most newly approved medications have strict temperature control and handling requirements. Yet according to a 2019 IQVIA Institute study, the pharmaceutical industry loses around $35 billion annually for temperature-related product issues. With mRNA-based treatments accelerating along with precision medicine and other biologic drug discoveries, the need for strict thermal control will only increase in urgency.

ENSURING PATIENT SAFETY AND OPTIMAL OUTCOMES

The traditional pharma manufacturer control tower has received recognition across the ongoing Covid landscape for its ability to proactively identify upstream issues such as active pharmaceutical ingredient (API) shortages, or downstream issues such as delays leading to possible temperature excursions. Real-time data from carriers, IoT enabled devices, suppliers and more, feed the control tower construct not unlike how real-time flight status updates inform operators in an air traffic tower.

This process of surfacing, normalising and aggregating data creates a framework for identifying problematic events, and a foundation for generating actionable insights – but what actions and when? Defining these events or thresholds that should be acted upon by an authorised operator is another important piece of a control tower implementation. As an example, a user that is alerted to a delayed delivery of a medical device for a patient's scheduled surgery should be empowered to intervene if the delay may lead to a cancelled procedure.

The goal of each intervention is to seamlessly enable the best patient outcome. In the above scenario, the intervention could consist of placing a call to the clinic to simply communicate the delay – though in another scenario, the operator would procure a replacement product with overnight delivery while simultaneously retrieving the delayed package for return to the manufacturer.

DOWNSTREAM EFFECTS OF EXCURSIONS

In another example, consider the cancer patient waiting for the delivery of post-chemotherapy medicine to stimulate the generation of protective white blood cells. If this expensive medicine were to be delayed, the patient would likely need to go to a clinic to receive the injection – an inconvenient trip and more expensive delivery site that places the patient in a public setting while immunocompromised. The worst-case scenario is a package of this important therapy sitting outside, in the heat, while its efficacy starts to wane yet the patient, feeling weak, sick, anxious – takes it as directed and yet still ends up admitted to the hospital with an infection because the medicine was degraded by the extreme heat and melting coolant.

This is why the most impactful supply chain control towers are comprised of a robust intervention program. By prioritising the removal of any potentially impacted therapy from last mile distribution, no patient ever receives a subpar therapy whether it be medication to treat an ailment, or a vaccine to prevent illness onset. And in this era of heightened vaccine hesitancy spurred by Covid, deploying control tower capabilities to eliminate degraded therapies from the medical ecosystem may assuage lingering concerns related to product authenticity or condition.

A COLD CHAIN CONTROL TOWER IN ACTION

In early 2021 as the mRNA-based Covid-19 vaccines were being deployed to elderly residents of long term care homes, the media focus was primarily on the supply of doses and how to prioritise recipients. Beyond the actual vaccine vial, other administration supplies were required to deliver the injections such as syringes, PPE, dry ice and alcohol wipes. As clinicians were focused on keeping the rate of vaccination high, there was little time to source supplies – yet without these accessories, vaccines could not be administered.

The urgency of this situation, and the sheer number of entities involved generating data feeds, lent itself to the fail-safe nature of a supply chain control tower. After needed vaccine supplies were sourced for replenishment, every single shipment was tracked to alert an operator around unexpected carrier status changes. At the first sign of a potential delivery failure that could cancel a vaccination clinic or lead to wasted doses, an operator intervened. This happened with nearly 5% of all shipments due to weather delays, package mis-sorting and damage. The alerting system would identify the issue and the operator would intervene based on the need and severity. Over the course of this program, more than 2,000 product replacements were swiftly sourced and delivered, enabling the ongoing delivery of lifesaving vaccinations.

DRIVING TOWARDS AUTONOMY

At the outset of a supply chain control tower deployment, decision making is reactive based on alert logic. However, over time as data accrues, patterns emerge that might point to discrete sources of risk that would otherwise take longer to crystalise. A good example here is lane performance analysis. As data reveals that specific shipping lanes are high-risk based on intervention history, problematic lanes can be discontinued and replaced with lanes that are high-performing based on their on-time history. And as lane performance and confidence increases, there may be opportunities to optimise packaging for longer duration, lower cost shipping.

KNOWLEDGE IS POWER

The introduction of the Covid-19 vaccine illuminated the therapeutic cold chain for many consumers that had never previously pondered how therapies are packaged, shipped and stored. Further, given the impact of Covid on supply chains across nearly every industry, the need for the real time visibility has never been more evident: according to Gartner, supply chain visibility is the top funded investment initiative prioritised for nearly 50% of organisations. Over time a robust control tower can reduce problematic scenarios, drive better efficiency and inform decision making while the remainder of supply chain activities seamlessly execute – all with the goal of better patient quality of life.

> **By prioritising the removal of any potentially impacted therapy from last mile distribution, no patient ever receives a subpar therapy whether it be medication to treat an ailment, or a vaccine to prevent illness onset**

THE *FIGHTBACK* AGAINST COUNTERFEIT ONLINE MEDICINE SUPPLIERS

Denny Bros on the dangers of using online medicine suppliers and the safety measures that companies are using to fight counterfeit medicines.

We have all read about – and probably participated in – the boom of online shopping during the last 18 months.

The under-pressure healthcare sector is no different with national reports claiming there has been a clamour by patients who have no choice but to turn to online pharmacies. In fact, according to the Pharmaceutical Journal, the number of items dispensed from distance-selling pharmacies, including online dispensaries, increased by 45% due to the Covid-19 pandemic.

But this in turn means patients could be at threat of a multitude of problems including taking the right medicine, but wrongly, or taking medicine and having no way of knowing whether it is genuine.

While falsified medicines is not a new thing, the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) believes one in 10 people now use online pharmacies.

And the International Anti-Counterfeiting Group has estimated that the Covid-19 pandemic has led to growth in falsified medicines of around 25% between 2019 and 2020. This increase in criminal activity – and the statistics around it - are deeply worrying.

Indeed, the NHS has referenced the dangers patients are at risk of when using online pharmacies. Medicines ordered online can be diluted, fake, or out of date if bought from an online pharmacy which isn't legitimate. And whilst patients can look out for a logo of authenticity from the General Pharmaceutical Council, the logo's use on registered pharmacies' websites is entirely optional, meaning there is a chance that users can be left unaware if they're using a legitimate, registered pharmacy.

SO WHAT CAN BE DONE?

There are a range of pharmaceutical labelling solutions that support compliance with the Falsified Medicines Directive (2011/62/EU) regarding packaging for prescription drugs and high-risk, over-the-counter medicines. These include tamper-evident labels and incorporating unique serial numbers to identify and authenticate individual products. Other measures include making labels coin reactive so a coin is rubbed over the surface to reveal what is hidden beneath or adding a now-common QR code. Silver foil can be added to a product to make it more challenging to counterfeit while "hickies" can be deliberately printed that a counterfeiter may not think or know to replicate.

> "These safety measures are becoming more state-of-the-art and unrecognisable all the time."

These safety measures are becoming more state-of-the-art and unrecognisable all the time.

Print features to help combat counterfeiting also include a security 2D matrix which enables information to be encoded using either text or numeric data. Microtext is another solution offered enabling words to be printed below or at one-point size which is almost unnoticeable to the human eye without the help of magnification.

Labelling forms a crucial part in this "fightback" against counterfeit online medicine suppliers.

With the pandemic and Brexit adversely affecting the supply chain, it has never been more important to protect the authenticity and safety of the pharmaceutical sector.

The latest trends in anti-counterfeiting packaging technologies and how Covid-19 has played a major role in product innovation.

IMITATION GAMES

Author:
ROY BUTCHER
- procurement manager at Southgate Packaging.

Over the past year, ensuring healthcare products are delivered to healthcare professionals and consumers safe and secure has been vital. While anti-counterfeiting technologies have long been an important component in the pharmaceutical supply chain, since the pandemic the demand has not only sky-rocketed but became a necessity.

Anti-counterfeit packaging is the process of assigning secure packaging to a product to minimise counterfeiting or infringement and in doing so, the product is then prevented from imitation and confirms the safety of the goods. In recent years the demand for anti-counterfeit packaging has continued to grow, with predictions that The Global Anti-Counterfeiting Packaging Market is estimated to develop at a rapid pace from 2021 to 2027.

There are two major factors that are influencing the adoption of anti-counterfeit packaging. The first is to protect from economical and reputational damage to a company. Such technologies automatically authenticate a product's genuineness and offer brand security, helping to eliminate potential fraudulent use of a manufacturer's brand image.

Secondly, and most importantly, anti-counterfeit packaging prevents potential consumer health risks. A factor that is becoming increasingly important as e-commerce pharmaceuticals see a huge growth, a change we have witnessed first-hand at Southgate.

While this has been a practice for some time now, since the start of the pandemic, 4.3 million adults across the UK have ordered medication online for the first time. There are various reasons why people have turned to postal deliveries for their medication, for example, for ease and convenience, to avoid making journeys to the pharmacy, and to prevent the risk of infection from Covid-19.

One factor that is making one of the biggest shifts in pharmaceutical distribution right now is that more and more consumers are now buying over the counter (OTC) products that are non-controlled online. Around 80% of drugs used in day-to-day life can be ordered online now and consumers are embracing e-commerce as convenient access to them. This started pre-Covid, but the pandemic has certainly played a role in the rise, and now the responsibility lies to distributors to meet this new demand. It will be interesting to see if this shift in consumer behaviour is set to stay in the long-term and if so, how this will shape pharmaceutical packaging designs.

While the process of selling pharmaceuticals online and distributing direct to the consumer presents a high risk of counterfeiting, it is not the sole reason for concern. Many packaging companies are also receiving requests from companies where their medicines have experienced counterfeit through traditional distribution channels. The inability to know for certain if a patient has received a genuine product is then a major issue for medical professionals.

Ensuring pharmaceutical products are delivered from factory to patient in a safe yet efficient manner is an intricate operation with many components to consider. Complex restrictions and performance requirements must be met, all while ensuring it is protected and untampered on its journey. As a result, packaging companies are playing a pivotal role by introducing the latest technologies and new ways of manufacturing, assembling, filling, and sealing pharma products to ensure successful and secure end-to-end delivery.

“While the process of selling pharmaceuticals online and distributing direct to the consumer presents a high risk of counterfeiting, it is not the sole reason for concern.

At Southgate, we design our products with safety at the forefront. Last year, we wrapped up five million NHS Covid-19 home testing kits using our range of self-seal bags to minimise the danger of excessive handling and contamination. Our design meant that the tests could be quickly and efficiently sealed and sent out to people who are unable to attend test sites.

Looking ahead, the continued growth of e-commerce pharmaceuticals will certainly present new and lasting challenges for both the pharma and packaging industry. The need for multi-layered protection technologies that can be easily and effectively integrated into packaging will become increasingly important as a means of securing both pharmaceutical brands and the consumer.

Counterfeiting continues to be one of the most serious threats faced by the pharmaceutical industry, causing damage in terms of consumer health, economic health, and public trust in healthcare systems. Undoubtedly, designing and specifying the packaging used throughout the end-to-end supply for medicines is a complex challenge and the packaging specialist's role is a difficult one. Yet our role is becoming ever more important as we set to meet new consumer requirements and increased demand. Working together with both the pharma industry and educating the end customer, we can fight the ever-increasing risk over the next few years.

JUST HOW *EFFECTIVE* IS FMD LEGISLATION?

How the key requirements of the Falsified Medicines Directive are being fulfilled by stakeholders and manufacturers.

The Falsified Medicines Directive (FMD, 2001/83/EC as amended to 2011/62/EU), and its delegated regulation EU 2016/161, together set out the requirements that manufacturers of human medicinal products must meet, as part of their legal responsibility.

This applies throughout the EU and responsibilities extend to wholesalers, dealers and parallel importers. Requirements came into force on 9 February 2019, with a number having already been implemented over the past two to three years.

WHY IS PREVENTING FALSIFIED MEDICINES IMPORTANT?

There are several types of falsified medicines. They include any medicine that is not made by the approved manufacturer, or contains too much, too little, or no active ingredient.

It might also contain another or an undeclared active ingredient – or has passed its expiry date. Items that are deliberately mislabelled, have fake packaging, or are in some way not as the authorised manufacturer intended, are also on this list.

All of these can have a critical impact on the safety of patients. There have been many documented cases of harm – including death – caused by falsified medicines, which further underlines the importance of robust control measures to protect patients.

Probably the first, and very well documented, example of falsification was the use of sulphanilamide elixir intended to 'cure sore throats like never before'.

The product used a diethyl ether as a solvent, that we know to be toxic to humans – resulting in hundreds of confirmed deaths. This event also sowed the seeds of the regulations and legislation to regulate and control modern medicines.

A more recent example of falsification is 72,000 packs, containing 2.1 million doses of three medicinal products, with a retail value of £4.7 million. Only around 40,000 of these packs were seized, with the rest likely to have been distributed.

The Medicines and Healthcare products Regulatory Agency (MHRA) regularly sends notifications of product theft – and access to bona fide packaging, labelling, serial numbers and batch numbering facilitates this illegal trade.

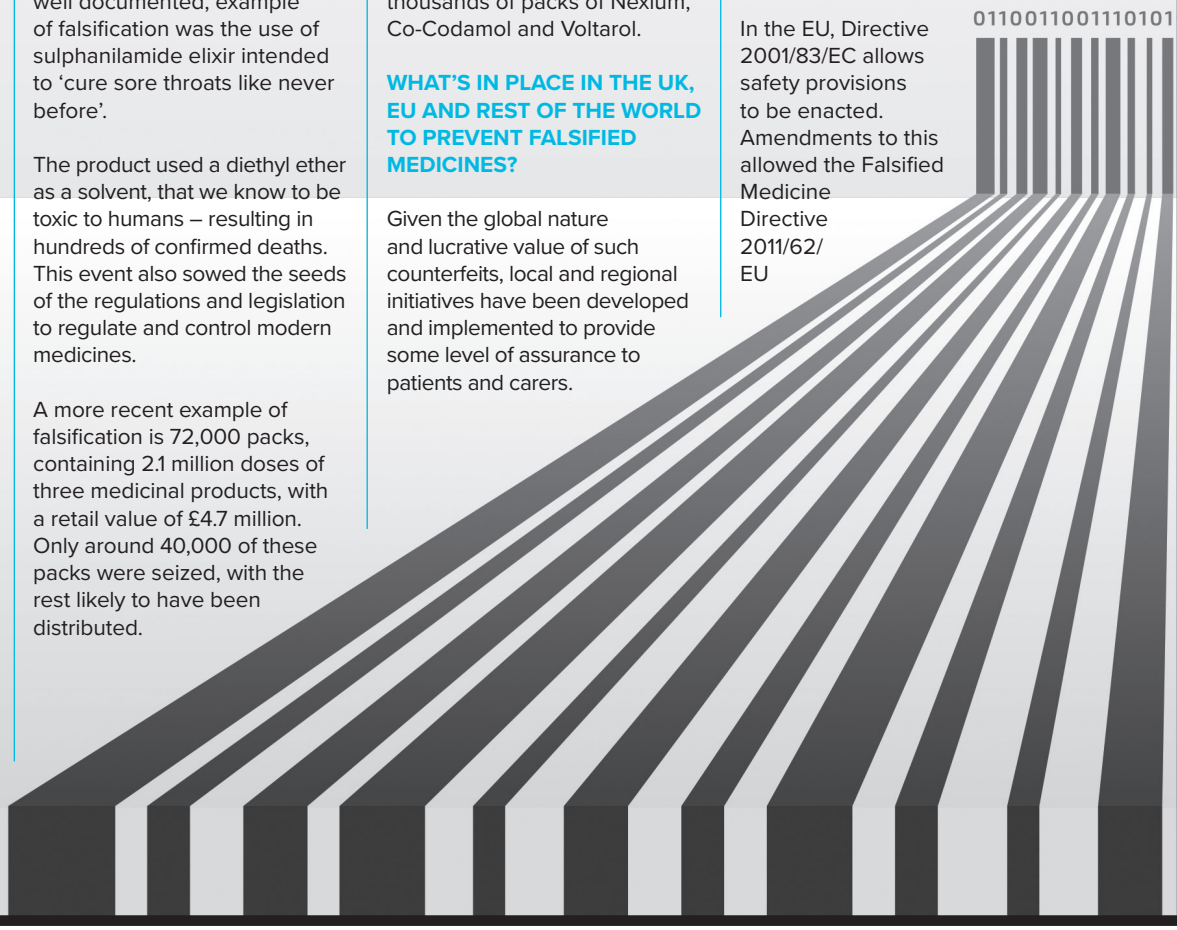
Some of the products affected recently have included thousands of packs of Nexium, Co-Codamol and Voltarol.

WHAT'S IN PLACE IN THE UK, EU AND REST OF THE WORLD TO PREVENT FALSIFIED MEDICINES?

Given the global nature and lucrative value of such counterfeits, local and regional initiatives have been developed and implemented to provide some level of assurance to patients and carers.

These include a relatively simple application of codes by legitimate manufacturers, that are scratched off by customers to reveal details that can be texted to a central data centre, verifying products' authenticity. This system was launched in several African countries in 2009, and to date has seen over 28 million verifications.

In the EU, Directive 2001/83/EC allows safety provisions to be enacted. Amendments to this allowed the Falsified Medicine Directive 2011/62/EU



to be defined with the key safety requirements. These came into force with the Delegated Regulation EU/2016/161, implemented by 9 February 2019.

This system is active and in place throughout the EU, but following Brexit, the UK may no longer be able to access the database that manages serialisation and coding of legitimately manufactured pharmaceuticals.

SPOTTING AND STOPPING FALSIFIED MEDICINES

Falsified medicines are notoriously difficult to stop and identify. With many tablets looking identical, the most effective way to spot illegitimate items is through small differences in packaging and labelling.

This can involve official routes, such as customs and border controls, but also the supply chain including wholesalers and warehouses. Similarly, the MHRA operates a 'yellow card' scheme whereby patients and carers can report discrepancies and adverse events directly.

Once such events are logged, the agency will undertake investigations such as chemical analysis – and in extreme cases, product recalls.

HOW PREVALENT ARE FALSIFIED MEDICINES?

After almost a year following its implementation, SecureMed – the EU body tasked with issuing serial numbers – noted that over 45 million medicines had been issued in the UK, and that there were no cases of any falsification.

This is a clear indication that FMD measures have very effectively halted this trade in the EU and UK. However, this is not the case in the rest of the world, where such measures don't exist – and may not continue to be the case for the UK if its pharmaceutical industry and MHRA are not allowed continued access to the SecureMed databases.

TRENDS FOR THE FUTURE

In the EU, FMD legislation will continue to be enforced, to safeguard the quality, safety, and effectiveness of medicines. Meanwhile, it's inevitable that those motivated to act fraudulently will continue to find ways in which the current system can be 'beaten' – and as with all regulations, FMD legislation will continue to be updated and refined.

The situation in the UK is less clear. Following the implementation of FMD – and before Brexit – there was clear evidence of the elimination of falsified medicines entering the country. However, this has depended on access to the EU databases.

If this continues, Britain will continue to benefit from safe and effective medicines. If, however, Brexit means the UK is denied access, then industry and regulators will need to develop and implement alternative systems to mitigate the risk of falsified medicines.

In conclusion, the FMD has gone a long way to assuring patient safety and product efficacy. Manufacturers and stakeholders have, in the meantime, responded positively. However, while this system will continue to be implemented in the EU, the position for the UK is much less certain.

Author:

DR ASH RAMZAN

- founder and principal consultant at regulatory affairs consultancy, Woodley BioRegcs.

> **"Given the global nature and lucrative value of such counterfeits, local and regional initiatives have been developed and implemented to provide some level of assurance to patients and carers."**

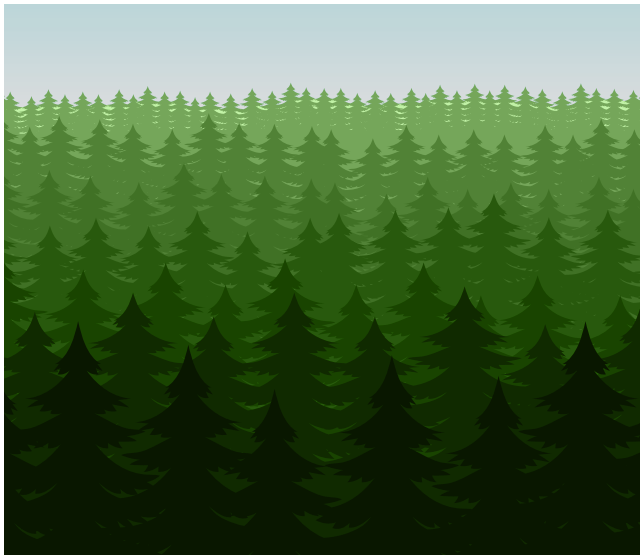
LEADING THE CHARGE TOWARDS SUSTAINABLE HEALTHCARE

There has never been a more important time to focus on sustainability as a nation and as an industry. The recently released UN climate change report shows we're at a tipping point in history. But it's not just carbon emissions that the healthcare industry should be focused on – sustainability needs to be at the core of every decision and strategy in the NHS and our sector as a whole. This can be achieved through process, procurement and innovation.

The NHS aims to be carbon neutral by 2040 on the emissions it controls directly and has set a target of 2045 to be neutral on the emissions it influences. These are ambitious yet important goals, as reducing carbon emissions represents an important step in fighting for a more sustainable future. But across the healthcare industry, there is plenty more that can be done.

THE HEALTH OF THE NATION

Moving towards a more sustainable healthcare system in the UK won't just reduce carbon emissions and help to mitigate the impact of climate change. It will also improve the health of the entire population. The environmental and societal aspects of the world have a direct impact on our health and affect long-term conditions.



Author: **HELEN DENT** - chief operation officer, at BIVDA

> **Issues such as the use of plastics, food production and air quality are all inextricably linked to cancer, respiratory illnesses, diabetes, high blood pressure and mental health conditions**

Issues such as the use of plastics, food production and air quality are all inextricably linked to cancer, respiratory illnesses, diabetes, high blood pressure and mental health conditions. As an industry we can lead the way in championing more sustainable, lower-carbon, and zero-waste solutions that will help to prevent these conditions. The diagnostics and pharmaceutical industry is one of the first ports of call when it comes to dealing with serious diseases. Technological advancements have led the way in detecting and treating these illnesses, now it's on us to think about how we can operate at a more sustainable level long term.

This isn't just about reducing our carbon emissions; this is about truly working sustainably. The entire pharmaceutical sector can work together to find more environmentally and health concise ways of working.

THE NEXT STEPS

The diagnostics industry strives to innovate, finding ways to identify and diagnose some of the world's deadliest diseases and health conditions. Innovation is our day-to-day and we need to apply that same creativity and drive to working more sustainably.

While the carbon neutral targets set by the NHS are a great start, we can do more than just responding to a number. Not only should we be leading the way in bringing that 2045 goal much closer, but we should be looking beyond carbon neutrality.

That's why this year BIVDA launched a Sustainability Training Program for all of its members. Sustainability is a key issue of operational transformation that the in-vitro diagnostics (IVD) sector must take heed of in light of the NHS Net Zero requirements, our collective corporate social responsibility and the duty we all share to protect the environment. As the trade association for the IVD sector, we're proud to champion the sustainable charge and help empower and facilitate businesses on their journey towards enhanced sustainability.

A Human Factors sampling strategy for platform devices.

FULL COVERAGE

Drug delivery devices for self-administration must go through compulsory human factors (HF) studies before reaching the market, to help identify and eliminate any risks the device may present to the end user. These tests are carried out on a sample population reflecting the device's intended users to best predict problem areas. With platform devices, however, the intended patient profile is unknown, given the device's versatility across a range of therapy areas. In this case, the device must be suitable for use across a wide demographic, covering varying physical and cognitive abilities as well as a range of ages. An inclusive strategy is therefore required to achieve thorough testing. The purpose of this article is to outline a useful sampling strategy which can be used as a framework for manufacturers to carry out user evaluation without identification of a specified user group.

Selecting an appropriate sample size is the first step towards building a representative test group. In the early stages of development, a sample size of five to eight participants per distinct user group is considered good practice, while at the validation stage, it is recommended by US and UK regulators to have 15 to 20 participants per user group. However, the number of user groups can vary and is likely to be higher for platform devices given the wide range of potential users. At Owen Mumford, we suggest dividing subjects into seven user groups to best cover the range of characteristics which could affect how end users operate a device (see table below).

The first four user groups represent people who may handle the device as a patient or to assist the patient. The remaining three user groups cover different perception, cognition and action (PCA) levels. Ideally, each use-impairment group must be mutually exclusive to get the best results. However, some overlap may prove helpful, for instance including people with both biomechanical as well as neurological impairments within the 'Action ability' group (see row 7). To get the best representation, each group can be further divided into sub-sections such as gender, ethnicity and hand dominance. Breaking down each group in this way may help identify the root cause when difficulties arise, allowing potential corrective action to be taken with the device design or instructions for use.

The sampling strategy outlined above can act as a valuable framework for manufacturers carrying out Human Factors (HF) studies for platform devices. An effective sampling strategy is critical to assessing risk across the range of possible users, and anticipating the needs of future customers in the most cost-effective manner. Comprehensive testing not only enables product designers to make informed decisions about a device but also assures business partners that any usability-related risk factors have been identified and dealt with during development.

Human Factors Sampling Strategy for formative studies

Group	Description	Minimum sample size	
		Small study (e.g. early stage evaluation)	Large study (e.g. late stage evaluation)
1. Adults	Adult aged 18 years plus; no upper age limit.	3	7
2. Juveniles	Persons aged between 8 and 17 years.	2	7
3. Caregivers	Lay caregivers who help another person to administer their injected medication.	2	7
4. Healthcare Professionals (HCPs)	HCPs who administer injected medication to patients (e.g. nurse, pharmacist, GP).	2	7
5. Perceptual ability	Persons with visual impairment. Plus at least one with auditory impairment.	2	7
6. Cognitive ability	Persons with a range of moderate cognitive impairment (e.g. ADHD, autism, dyslexia, learning disability).	2	7
7. Action ability	Persons with a range of physical (upper limb) impairment (e.g. RA, Parkinson's, MS).	2	7
	Total	**15**	**49**

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2021 FORUM
END-TO-END
SUSTAINABLE PMDI
SOLUTION

20th - 22nd
September

Sustainability in Inhalation Products –

The first End-to-End Sustainable Pressurised Metered Dose Inhaler (pMDI) Forum held on 20th - 22nd September 2021

The first End-to-End Sustainable Pressurised Metered Dose Inhaler (pMDI) Forum, co-organised by Pharmaserve NorthWest and Aptar Pharma, took place on 20th - 22nd September 2021 at Hurlston Hall, Lancashire, United Kingdom.

Pharmaserve NorthWest, an expert contract developer and manufacturer specialising in high value niche products, and Aptar Pharma, a global leader in pulmonary drug delivery device solutions, brought together speakers, participants and delegates associated with and involved in the field of pMDIs, from scientific, engineering, pharmaceutical and clinical backgrounds. The objective of the End-to-End Sustainable pMDI Forum - the first event of its kind - was to facilitate discussions on the use of new propellants and other technological innovations that can support sustainability in the area of pMDIs, and to enable the continuation of collaboration between these disciplines to bring about a lasting transformation in this space.

The Forum, chaired by David Wyatt from Aston Particle Technologies and Dr Geralt Williams, Director Scientific Affairs at Aptar Pharma, opened with a presentation from Dr Alex Wilkinson, a Respiratory Consultant from Lister Hospital in Stevenage. Dr Wilkinson is a member of the NHSE/I inhalers working group and spoke about the dilemma facing clinicians when needing to prescribe drugs that are essential to meet patient requirements and needs, but also do not pose a threat to the environment. Dr Wilkinson explained that a total of 8.4 million tonnes of CO_2 is produced annually due to the use of salbutamol inhalers[1].

Dr John Pritchard, a private consultant specialising in strategic approaches to developing respiratory devices, drugs and digital health, who sits on three Scientific Advisory Boards, spoke about Global warming from “greenhouse gases” and the contribution that is made by the Fluorinated gases, including HFCs. HFCs account for 95% of F-gas emissions and pMDIs account for ~2 % of HFC emissions[2], which is 0.03 % of all greenhouse gas emissions. Dr Pritchard explained that the use of HFCs is now subject to several phase-down targets, i.e. the 1997 Kyoto protocol, the Kigali amendment to the Montreal Protocol (2016), and the American Innovation and Manufacturing Act (2020). Although pMDI emissions represent a small fraction of total F-gas emissions, they will become increasingly important as other emissions reduce, so having a pMDI propellant with a low Global Warming Potential (GWP) will become necessary.

Matt Tyler, Business Development Director from Pharmaserve NW, part of OBG, presented their Runcorn manufacturing facility’s unique end-to-end solution. It provides equipment and capability from lab scale through to high volume commercialisation, vast experience in product development, generic and new chemical entities (NCEs), supply product globally and lab scale ready for HFA-p152a and HFO-1234ze. Tyler provided details on the readiness programme in progress for up to 100L GMP, and ready-made alternative propellant programme from feasibility to commercialisation.

Jackie Green, Business Development Manager and Richard Turner, Sales Director from H&T Presspart presented on their developments in plasma technology, using fluorocarbon polymerisation (FCP) that is sustainable as

there are less CO_2 emissions, no harmful emissions, no solvent, and can help to reduce the amount of material per can by 30%.

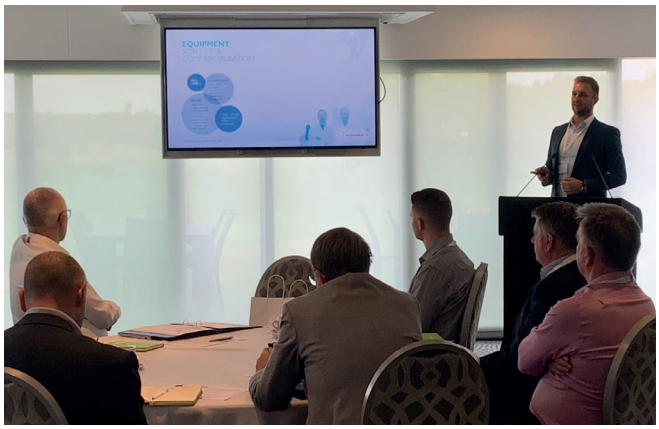
Andy Rignall from Pharmaceutical Technology & Development, AstraZeneca, was speaking on behalf of the International Pharmaceutical Aerosol Consortium (IPAC) and presented on the Evolving Legislative Landscape for Medical HFCs. Rignall summarised the current regulations governing HFC production and consumption, the ongoing process for their review, and how this creates the impetus to innovate pMDIs using low GWP propellants so that this delivery platform remains an available option for patients who need or prefer it. He pointed out that lessons learned during the transition away from CFCs include the need for collaboration across all stakeholders to ensure that continued patient care is the priority, to encourage innovation and to allow sufficient time for research and development activities. He recommended input from multiple stakeholders to minimise the impact of inhaled therapy across the whole product lifecycle and during the patient healthcare pathway.

Aptar Pharma's presentation by Dr Geralt Williams confirmed that alternative pMDI solutions are on the horizon to significantly reduce the pMDI CO_2 footprint, but also highlighted the need for industry-wide cooperation in order to have a successful transition to low GWP pMDIs, adding, "We must consider the needs of the patient as their journey is a complex and emotional process, as well as the resultant impact on the wider Health Care System".

Paul Sullivan from D.H. Industries Ltd presented on Sustainable pMDI Filling. He stated that the new propellants with low GWP can easily be handled on new equipment and installations. Sullivan also spoke about the UK standards for filling aerosols with flammable propellants, from The British Aerosol Manufacturers Association (BAMA) and international standards including the European Aerosol Federation (FEA) for Europe and national guides for other countries including the USA.

Analytical Strategies and Best Practices for Product Reformulation Submissions was presented by Mark Parry, Technical Director at Intertek, where he explained the various analytical techniques that are used to measure the chemical and physical properties of the formulation, alongside the bioequivalence performance and microbiological assessment.

Nayna Govind's, Verona Pharma plc, presentation was on Making the Switch to Greener Propellants "Regulatory Food for Thought". She summarised that switching from HFA 134a/HFA-227 to greener propellants is more complex than 'generic' inhalation development and can impact both pharmaceutical and therapeutic performance. There needs to be early engagement with appropriate regulatory authorities to better understand: the requirements for product specific preclinical



studies, the expectations for demonstration of pharmaceutical and therapeutic equivalence, the requirements for product specific clinical efficacy and safety studies, and the refinement of development strategy/costs/timelines on basis of regulatory expectations.
Greg Anderson from Pharmacentric Solutions Ltd, finished the meeting with his presentation on Sustainability in the Life Sciences and UK Drivers. He detailed the MMIP (Medicines Manufacturing Industry Partnership) Manufacturing Vision for UK Pharma[3] drivers, which features the 12 principles for green chemistry that should be applied across all medicine manufacturing platforms. The plan for delivering a "Net Zero" National Health Service[4], which states the importance of the supplier alignment to Net Zero commitments, and low-carbon substitutions and product innovation. He concluded his presentation with a list of prospective opportunities to discuss and explore at future forums and events.

Overall, the consensus from the Forum was that a transition to new, more sustainable propellants is key for the future of pMDIs. The best way to achieve lasting sustainability transformation is through discussion and collaboration, which we look forward to continuing in future Forums.

To keep up to date on these subjects, contact:

Pharmaserve North West:

Discover more about our capabilities:

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Aptar Pharma:

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1 Wilkinson AJK, Menzies-Gow A, Sawyer M, et al. An assessment of short-acting β2-agonist (SABA) use and subsequent greenhouse gas (GHG) emissions in five European countries and the consequence of their potential overuse for asthma in the U.K. BTS Oral Abstract No: S26. http://dx.doi.org/10.1136/thorax-2020-BTSabstracts.32

2 https://www.epa.gov

3 Manufacturing Vision for UK Pharma – Future Proofing the UK Through an Aligned Technology and Innovation Road Map. Medicines Manufacturing Industry Partnership. July 2017.

4 Delivering a 'Net Zero' National Health Service. NHS England. October 2020.

The considerations to make when manufacturing formulations for dry powder inhaled products.

TAKE A BREATH

The use of dry powder inhalers (DPIs) to deliver drugs have traditionally been focused on treating respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD), as the pulmonary administration of the active ingredients provides direct and rapid action.

DPI products are a combination of the active pharmaceutical ingredient (API), formulated with excipients and carrier molecules, within a device. The design and development of these must be conducted in symbiosis, as each directly impacts upon the other. Only when the drug substance can be delivered effectively by an appropriate device can the drug be seen to be successful; however, the implications for commercial manufacturing of products should be considered as early as possible within the design, to ensure that the drug's efficacy is matched by economic viability.

EARLY PHASE MANUFACTURING DEVELOPMENT

Challenges to meet manufacturing demands in early phase development usually involve the supply chain for device components, excipients, and APIs. Establishing a strong team to project manage and ensure equipment and material is available to meet project timelines is crucial, allowing performance to be measured and the procurement of additional equipment and resources at speed if necessary.

Early phase development provides the opportunity to capture critical data, which can then be evaluated for later phases. The equipment used and processes developed should be synergistic with those to be used in scale-up – this reduces the required data capture for defining the critical process parameters (CPPs) and critical quality attributes (CQAs). Avoiding duplication of tasks allows time to be used effectively to gather data for quality assurance and GxP requirements, and involving late-stage manufacturing experts in the development teams can assist in streamlining processes.

FORMULATION MANUFACTURING

The majority of DPI formulations are a mixture of API and a carrier excipient to improve the performance of the powder. Force control agents, such as magnesium stearate, are added to reduce particle adhesion and improve powder flow. There are a range of blending approaches, characterised by the amount of shear applied during mixing, with more cohesive particles generally requiring higher shear forces for mixing.

Low-shear blending (e.g., tumble mixing) may be used for particles with low cohesion, or those that are more fragile or heat-sensitive. High-shear blending causes particles to impact each other or the wall of the mixer, allowing more cohesive particles to distribute evenly through the carrier excipient. The optimal blending approach will depend on the characteristics of the API. Maintaining uniformity is a key challenge for blending processes, especially since the blending parameters can affect the formulation's homogeneity and stability.

Particle engineering, such as spray drying, can be used to control the particle size, shape and density of components to produce formulations without the need for blending with carrier excipients. This can be particularly useful for high-dosage products where a blend would require too high a powder load, or for large molecules that require low-energy processing. Since the particle morphology is influenced by the spray-drying procedure, it is important to understand how processing may affect formulation performance during scale up, as there may be necessary controls and storage requirements to ensure consistency of delivery characteristics.

SCALE-UP CHALLENGES

There are many factors that impact the performance of a powder formulation and delivery device, so understanding these critical parameters early and establishing robust processes can mitigate the risks associated with scale

up, which invariably lead to reworking, costing both time and money.

A challenge that is particularly applicable to respiratory drug development is deciding what constitutes an appropriate scale of manufacturing at each stage of development. In early development phases, when materials are often in limited supply, there is an inevitable trade-off between the scale of manufacture and the number of batches that can be produced to build the necessary scientific understanding. Manufacture at the intended commercial scale involves large batch sizes, which can be time-consuming and expensive, and so is often not performed until the later stages of development.

Developing validated scale-up models in the early phases can demonstrate the ability to achieve comparable drug product performance from batches made at laboratory-scale and commercial-scale, so using equipment that is directly scalable from that used during early phase development, prevents unnecessary duplication in setting CQAs and CPPs. This allows a significant amount of the development work to be conducted in the laboratory at development scale, minimising material costs and enabling faster execution of experiments, whilst giving confidence in the ability to move to the larger scale at a later date. This also allows capital investment at any commercial supply manufacturing site to be made later, based on a risk-based approach for the project.

DEVICE CHOICE IMPLICATIONS

Device choice impacts the manufacturing of both the device and formulation, and DPIs can include either capsule- or blister-based platforms. Blisters offer enhanced light and moisture protection for drug products, with potential shelf-life advantages. In early development, capsule-based devices are favoured, as they offer flexible dosing and a relatively quick pathway to clinical phases. However, capsule developments can be complex, as dry powder blends can be influenced by the capsule material, and the interaction between capsule and formulation. Capsule composition, water content, lubricant level, and surface quality can all result in the formulation's physical properties.

Commercially-available capsules are primarily gelatin, or hydroxypropyl methylcellulose (HPMC). It is important to understand the characteristics of both formulation and device so that the most appropriate capsule type can be matched. In addition, tight control of manufacturing environmental conditions and long term packaging considerations are necessary to maintain stability and performance of capsule-based DPIs.

DE-RISKING SCALE UP

Simplicity is paramount, and reducing complex documentation is key to meeting tight deadlines for demand when drug shortages are being faced. The early adoption of Lean Manufacturing techniques ensures optimal utilisation of resource and equipment by identifying bottlenecks and constraints, as well as challenging existing set up, clean down and turn round processes to enable efficient capacity planning.

Planning in early stages for commercial requirements reduces the risk of having to spend time and resources reworking designs or processes, so involving experts with experience of commercial manufacturing at an early stage is vital.

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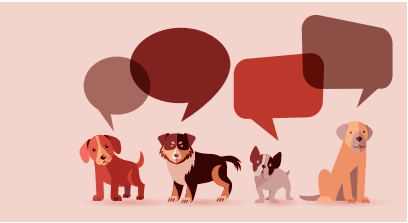
> **Only when the drug substance can be delivered effectively by an appropriate device can the drug be seen to be successful.**

Talking points



Competition launches to find ways to replace dogs in drug testing

A competition has been launched for tech innovators challenging them to create new ways to replace the use of dogs in certain drug tests.

The National Centre for the Replacement, Refinement and Reduction of Animals in Research's (NC3Rs) 'Virtual Second Species' challenge invites those in the tech industry to create 'virtual dogs' which scientists can use to predict the adverse effects of drugs before their first use in humans.

The aim is to find developers who can apply advanced computations and mathematical modelling approaches to develop a suite of virtual dog tissues and organs to model toxicological endpoints for New Chemical Entities (NCEs). These models will hopefully be able to predict the unexpected and detrimental effects of drugs on human health, particularly in major organs.

As of 2020, there were just over 2,000 experiments taking place in the UK which used dogs as part of their testing. Currently, regulation requires drugs to be tested in two species to monitor for issues: a rodent, such as a rat, followed by a non-rodent, such as a dog. However, this method does not always convey the adverse effect that will happen in humans, leading to wasted animal lives, time, and money.

WHO LAUNCHES GLOBAL STRATEGY FOR MENINGITIS

The World Health Organisation (WHO) and partners have launched a new global strategy to combat meningitis.

The Global Roadmap to Defeat Meningitis by 2030 was launched by a broad coalition of partners involved in meningitis prevention and control at a virtual event, hosted by WHO in Geneva. Its focus is on preventing infections and improving care and diagnosis for those affected.

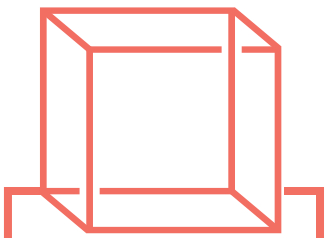
The organisations involved are hoping to save over 200,000 lives annually and reduce disability caused by meningitis. By 2030, the Roadmap hopes to eliminate epidemics of bacterial meningitis, reduce deaths by 70%, and halve the number of cases.

Part of the Roadmap's plan includes the development of new affordable vaccines for meningitis. Whilst there are already several vaccines that protect against the disease, the WHO states that not all communities have access to these vaccines and that many countries are yet to introduce them into their national programmes.

Meningitis occurs when membranes surrounding the brain and spinal cord become inflamed from a bacterial infection or a virus.

Meningitis that is caused by bacterial infection tends to be the most serious and can cause fast-spreading epidemics. It kills one in 10 of those infected – mostly children and young people - and leaves one in five with long-lasting disability, such as seizures, hearing and vision loss, neurological damage, and cognitive impairment.

OUTSIDE EPM



RwHealth founder and CEO Orlando Agrippa explains how AI innovation in emergency admissions from asthma and COPD will be essential this winter.

Make sure to read the full article on www.med-technews.com

BE SURE TO LISTEN TO

Reece Armstrong speaks to Professor Saad Shakir, director of the Drug Safety Research Unit about the organisation's work to monitor the safety of Covid-19 vaccines after they were approved for use.

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