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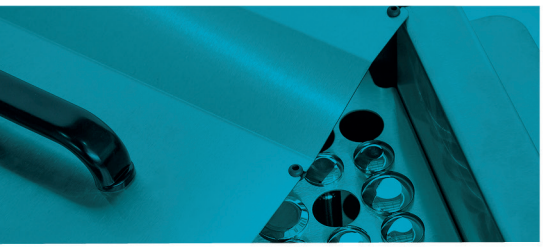

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CLOSING OUT THE YEAR

EDITOR'S DESK

JAI MCINTOSH

As we step into the final months of the year, a period of reflection is, in most cases, inevitable. Global turbulence has presented every industry with a unique set of challenges that have required patience, intelligence, and innovation to partly overcome. The pharma industry has played host to some outstanding developments with over thirty novel drug approvals and a continuation of effective vaccination programmes against Covid-19, with the World Health Organization recognising that, as of the 5th of November, 13,534,474,309 vaccine doses have been administered.

A result of the challenging global environment is that many companies have had to undertake large-scale job cuts in order to find some semblance of profitability. Big Pharma's Pfizer has committed to reducing $3.5 billion worth of spending, eliminating hundreds of jobs in the UK alone with 500 staff members at their Sandwich facility in Kent losing out, not to mention the job cuts the company enacted in Ireland too. This comes after the Company is expected to encounter larger than expected losses - evidenced perhaps by the 42% drop in the value of their shares. Pfizer is not the only one. Biogen cut roughly 11% of their staffing numbers in July (roughly 1000 jobs), PTC Therapeutics cut 25% of its workforce with the process still on-going. The list is rather depressingly endless. For those interested, Biospace.com has a live tracker monitoring these losses throughout the industry, well worth a look.

However, increased interest in new technologies, predominantly artificial intelligence and machine learning, have seen an uptick in investment with the UK Prime Minister Rishi Sunak committing "a further £100 million to accelerate the use of AI on the most transformational breakthroughs in treatments for previously incurable diseases." Companies globally are, despite job losses, looking to invest in the artificial intelligence space as competition for the most accurate advancements in pharmaceutical technologies heats up. We at EPM HQ expect AI to play arguably the most prominent role in pharma innovation throughout 2024.

Sustainability will also remain high on the agenda given the requirements to reduce carbon emissions. The pharma industry on the whole has made some positive steps towards this, however, there is plenty more to be done. The industry is overwhelmingly wasteful with its use of water and single-use plastics. More needs to be done to reduce carbon intense supply chains and logistics too. Manufacturing continues to be the biggest emitter, with roughly 70% of all pharma emissions coming from these processes. A restructuring of all of these processes is inevitable if companies are to fall in line with national and international carbon neutrality targets.

2024 will be fraught with challenges. Yet, in an industry governed by innovation there are many reasons to be hopeful.

CPHI Annual Report Predicts VC Capital (Re) entry and Contract Services Growth in 2024

New research from the CPHI Annual Report 2023, launched during CPHI Barcelona, points to an uplift ahead for biotech funding and a consequential follow through of growth for pharma contract services.

Analysis was provided by CPHI Report expert, Brian Scanlan of Edgewater Capital, who highlighted that liquidity in the biotech and mid-sized pharma market is typically a proxy of growth for the CRO/CDMO sector. Significantly, for the first time in 18-months funding into the sector seems to have stabilised over the past two quarters at levels seen just prior to the pandemic: "If we've already reached the bottom, then one level of uncertainty (risk) will be reduced, and more predictability can be factored into the future spending habits of emerging pharma. So will a belt loosening ensue in 2024?"

In fact, total funding into the sector through July is $30.2 billion and for the full year 2023 is trending well ahead of 2022. The only notable absence is in the continued weakness of IPOs, and this is exacerbated by clogged exits – i.e investors who saw a pathway to exit just two years ago are now stuck until the valuations come back to former levels.

Scanlan added that while there are still "too many emerging pharma companies vying for too little capital" the situation is now potentially changing. The number of companies with active R&D pipelines globally has grown from nearly 4,800 in 2020 to over 5,500 in 2023. That's an increase of nearly 15%, while funding levels have dropped to nearly half the 2020 levels during the same period. For CDMOs, the impact of this has been a short-term slowing of development pipelines, as biotechs look to maintain a financial cushion.

Scanlan predicts, however, that the market is now turning: "There are signs of an improving VC funding environment, but this needs to coincide with increasing pharma M&A and a healthier IPO environment. We believe softer demand, particularly from emerging pharma and in earlier phases of development, will extend for a period of 12-18 months. However, the investment banking community is already signalling a pickup on deal activity starting in late 2023 and accelerating into 2024."

The other significant (positive) macro factor for CDMOs is the well documented workforce shedding at big pharma we have seen in 2022 and particularly in the early part of 2023, which will almost certainly bolster demand for CRO/CDMOs in 2024. Therefore, Scanlan concluded that the long-term fundamentals for CRO/CDMOs are excellent given the number of compounds sitting in all phases of development, and continued market dynamics that favour increases in outsourced penetration rates in the coming years.

CPHI Annual Survey: Global Pharma Resilient with India the Chief Beneficiary of Macro Changes

In line with wider market sentiments, pharma confidence has dipped below the record scores of 2022, but has remained extremely resilient despite wider macro uncertainty. In fact, the CPHI Pharma Index – a collateralised metric of all small molecule categories in the survey – reported its second highest ever total, just 2.5% down on the 2022 all-time high. This highly positive result highlights the medium-term trajectory of the industry and the underlying strength of market fundamentals.

The United States unsurprisingly remained the top overall ranked nation (when evaluated across all criteria), with India continuing to make year-on-year inroads and looks well placed for significant growth in 2024 – particularly as the country moves from a generic focussed industry to one that increasingly supports global innovators.

In fact, India remained top of the 'growth category' for the second year running (scoring 7.8 out of 10) moving further clear of the United States. The country also saw improvements in its score for 'biologics quality' and finished only narrowly behind the USA for 'overall competitiveness'. Consequently, the report predicts India is undergoing an accelerating transformation from a generics hub to an innovation focused pharma economy, driven by the incremental steps of its largest CDMOs. India is also predicted to see the fastest CAGR in biologicals over in the next 5-years, as it quickly builds a bio CDMO base similar to those we have already seen emerge in China and Korea.

The report identified that many of the industry's growth drivers we saw in 2019 are still present, but are now supplemented by the breakthroughs in microbiome therapeutics, mRNA [of course], while AI now looks increasingly likely to drive new efficiencies for the industry over the next 5-years.

SUSTAINABILITY COMMITMENTS ACCELERATING IN PHARMA SUPPLY CHAIN

Sustainability goals and metrics are now being implemented across the pharma supply chain, with the rate of adoption accelerating quickly. A majority of CDMOs are expected to use them within the next 2-years, a significant shift from last year's survey when the expectation was that changes would take up to 5-years.

The rate of change is also increasing and 60% of executives forecast that innovators will require CDMOs to implement sustainability metrics (e.g. full waste recycling, green power use, low PMI targets, and/or green chemistries) as a part of contracts within the next 2-years. A further 20% anticipate that CDMOs will be expected to show ESG goals as part of any supplier deals, with just 20% believing that only 'cost and capabilities' will remain an innovator's single factor in assigning new contract decisions.

"The 2023 CPHI event in Barcelona is our greenest to date, but we are also increasingly using the event as a platform to centralise debate, propagate best sustainability practices, and help our partners accelerate towards greener manufacturing methods," commented Silvia Forroova, Director - Partnerships & Sustainability at Informa.

Looking deeper at the findings released from CPHI Barcelona, only 9% of the pharma companies stated they had 'no current green manufacturing activities'. The most popular initiatives currently in use across the industry are: 'waste and water reduction programmes' (40%); 'process improvement working groups' – including green chemistries, metal catalysis, continuous processing (33%); 'manufacturing equipment optimisation' – e.g. intelligent energy programmes and machine learning for process efficiency (32%), and 'decarbonising company supply chains' (29%).

Forroova added: "The trend in the industry is very clear, and we are seeing all supply chain partners exploring more efficient manufacturing processes. You only need a look around the show floor to see a proliferation of this type of approach – which also often brings cost benefits, as a more efficient process is typically cheaper. I would therefore encourage any company starting from material manufacturers to finish dose to read our report and attend best practice sessions. The rate of change is increasing rapidly and we expect this to be one of the biggest themes for manufacturing in 2024, as well as the fastest evolving. Getting ahead now will undoubtedly help in achieving competitive differentiation."

CPHI Pharma *Award Winners 2023*

CEO OF THE YEAR –
Enrico Zodio, Procos

API DEVELOPMENT & INNOVATION –
Snapdragon Chemistry, A Cambrex Company

FINISHED FORMULATION –
Lubrizol Life Science Health

MANUFACTURING EXCELLENCE –
Luminary Therapeutics

PACKAGING & MACHINERY -
Gasporox

SUPPLY CHAIN EXCELLENCE –
Catalent

REGULATORY COMPLIANCE –
Lambda Therapeutic Research

DRUG DELIVERY & DEVICE INNOVATION -
Medicsen

ACCELERATING INNOVATION –
REACT4LIFE

SUSTAINABILITY –
Schneider Electric

START-UP INITIATIVE –
InSyBio

AT THE HEART OF PHARMA –
Merck KGaA

CPHI BARCELONA: A REVIEW

Jai McIntosh

CPHI Barcelona was, for all intents and purposes, one of the most successful pharma events of the year. Having touched down in a sweltering mid-October in the Catalan capital, there was an unerring sense of optimism in the air. Navigating the city wasn't too easy given the sea of suits stampeding through the streets and the subways all trying to get to their stand, or to their meetings, within the Fira Barcelona-Gran Via.

The layout was close to flawless, and the array of companies each with their own USP was immediately impressive. Unsurprisingly for an industry this large, the event felt more like walking through a small corporate town than a standard industry event. With roughly 50,000 mostly coffee-fuelled individuals buzzing around driven by a desire to collaborate and innovate. The mood within every hall was overwhelmingly optimistic despite the plethora of issues that have impacted the sector throughout 2023.

Whilst all companies were there to ultimately drive business and uncover opportunities, there seemed to be universality in the way in which companies and individuals understood the demand on them to achieve sustainability goals, manufacturing quality targets, to find solutions to supply chain issues, and to be on the front foot of global innovation. It may not need saying, but the world relies on these companies and these individuals for the health of themselves and their loved ones. The importance of an event like this cannot be overstated.

The presence of big pharma was palpable, yet not overbearing. Most notably from our view at EPM HQ, we were hugely impressed with Bora Pharmaceuticals display and the conversations they were conducting. An interview that will appear on EPM online - part of our CPHI Interview Series - in the coming weeks with Bobby Sheng, CEO of Bora will, I hope, interest readers. Mr. Sheng touched on the rapid development of Bora, their manufacturing expansion, and their goals for 2024 and beyond. Yet, what struck most about our conversation, and the subsequent conversations we undertook across the week,

was the importance placed on building a healthy company culture and the fundamental significance of getting this right.

This seemed to be a prevalent motif throughout the exhibition, with many that we spoke with touching on the difficulties of finding and hiring the right talent. Somewhat to our surprise given the job cuts that have afflicted the industry throughout the year - see the Editor's note. That said, there is credibility in the notion that hiring the right staff, rather than hiring a lot of staff, may lead to improved financial prospects.

Sustainability was, rather unsurprisingly, top of the agenda for many of the companies there. There is oftentimes a level of discomfort surrounding pharma and sustainability given that the industry is more environmentally damaging than the global automotive industry, and when you account for the number of people simply flying in to take part in the exhibition, let alone the carbon costs of running the show and operating displays, the show itself may not be the most sustainable of events. The industry is well aware of the pressing need to decarbonise quickly, with the most confident of companies proudly displaying their year-on-year sustainability targets. Transparency is key, scrutiny also. It is undoubtedly the responsibility of the industry to ensure that these targets are met and adhered too.

The development and strong future prospects of the Indian pharma industry was prevalent throughout the exhibition, with the CPHI Annual Report stating that: India was widely seen as a global winner, executives from India have offered up the most positive outlook for 2024 – with 61% 'highly positive' and a further 37% 'moderately confident'. This result contrasts with a global average of just 37% 'highly positive' and 54% 'moderate' in all executives. For India, and for the industry as a whole, these developments will be key to future success.

There was also a strong focus on the formation of small-scale pharmaceuticals designed specifically for a small group of individuals who need catered care. Whilst this may seem like a commonsensical idea, the demand for large-scale pharma production often prevents smaller-scale medication from being produced. This was one of many facets of the exhibition that engendered a sense of hope for the future landscape of the pharma industry.

CPHI Barcelona lived up to its slogan: the heart of pharma. The industry is needed more than ever, yet there is a requirement on the industry to adapt and change to the demands of the contemporary and the future. Ultimately, most left optimistic, and rightly so.

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THE BEST STRATEGIES TO MODERNISE PHARMACEUTICAL QUALITY SYSTEMS

Author: Sofia Lange, DIRECTOR OF STRATEGY, VAULT QUALITY & MANUFACTURING, VEEVA SYSTEMS

Despite individual regulatory bodies having their own unique set of requirements, for most organisations, the challenges associated with annual product quality reviews (APQR) are largely the same. Issues with fragmented systems and paper-based processes prove increasingly burdensome.

APQR is essential to ensuring consistency of production processes across product lines, assessing the appropriateness of specifications and identifying opportunities for improvements. Due to the complexity of gathering the necessary information, organisations may undertake these reviews with the goal of merely meeting the regulatory obligations. This often means they are missing out on opportunities to make improvements across the board.

COMMON APQR CHALLENGES

To demonstrate good manufacturing practices (GMP) compliance, quality teams spend a significant amount of time compiling the information required by the authorities for the APQR. This often means that important analysis of trends and identifying opportunities to improve the product and processes is left behind.

To ensure inspection readiness and achieve operational excellence, here are four ways to streamline common APQR pitfalls:

Limit manual, paper-based processes: Many quality assurance teams still manually compile reports and review information from paper or legacy systems. This is not only time-intensive but increases the chance of human-error occurring, which puts data integrity at risk.

Hold third-party partners accountable: Contract manufacturers or other external partners can make gathering information for product quality evaluations even more challenging. It is important for partners to outline obligations for completing the APQR via contracts or quality agreements. If not well defined and established in advance, quality teams have no choice but to rely on downloading and manually reviewing data and documents from partners, resulting in increased complexity.

Unify your data: By enabling greater communication among quality systems and expediting data gathering and sharing, enterprises can ensure proactive management of quality. Ultimately, data integrity is compromised when businesses use a multitude of systems, spreadsheets, and paper. By avoiding working across fragmented QMS, ERP, MES, LIMS, and other systems, APQR systems can be readily streamlined.

Monitor your progress in real time: Despite progress being measured against the annual APQR plan, usually there is a lack of visibility when it comes to the progress of information gathering for different sections of different products. Detailed metrics can provide transparency related to how mature an organisation is and may help to allocate existing resources. Teams using this information have the capability to create Corrective Action and Preventive Action Plans (CAPAs) for ongoing improvement.

MODERNISING YOUR QUALITY SYSTEMS

An effective way for businesses to streamline the execution of APQRs is by utilising unified quality systems with features such as review workflows, document production based on report data, and open APIs that make it easy to integrate with other applications. This enables organisations to implement a system that brings together data and workflows for alignment with external partners and real-time visibility while maintaining data integrity.

When looking at an advanced quality solution, there are several essential functions that will result in smooth APQRs:

Templates: A customised APQR table of contents can fit the requirements of various products and geographies. These templates can specify the exact type of content or APQR report items necessary for inclusion in the final report.

Automation: By automating procedures and generating

trend reports, you can ensure access to key information, while reducing reliance on paper. Data quality and compliance can be improved by automatically producing APQR templates, documentation, product-specific trend reports and binders when gathering necessary data.

Role-based task assignment: Streamlining execution enables authorised users to generate APQR records directly from the template. Role-based access streamlines review and approval processes and promotes accountability, ownership and traceability.

Workflows: Each section of the APQR can be assigned to a dedicated team and can be individually followed upon completion. This saves time by enabling parallel completion, allowing detailed oversight and promoting active engagement across functional teams. A modern system is essential to providing thorough audit trails that can lower compliance risk and improve data integrity while allowing careful monitoring of GxP (good practice) requirements.

Digital APQR binder: The automated creation of a digital APQR binder can be transformational for quality teams and regulators who need to examine papers. This binder contains all content referred to in the template, without the use of paper or spreadsheets. Easier access and verification therefore create a smoother review overall.

THE POWER OF DIGITAL QUALITY PROCESSES

By implementing digital tools and procedures, companies can reduce the manual, dispersed, and paper-based APQR processes commonly used. A unified system on one platform empowers increased efficiencies by allowing data flow, real time reporting, and process automation. By taking a unified approach, organisations can easily combine APQR data from several sources, enable simultaneous execution, and obtain confidence that information is correct and readily available. Ultimately, this allows businesses and regulators to enjoy a smoother and more collaborative APQR experience while focusing on desirable continuous improvement outcomes.

> By implementing digital tools and procedures, companies can reduce the manual, dispersed, andpaper-based APQR processes commonly used.

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UNDERSTANDING TABLET PRESS WEAR

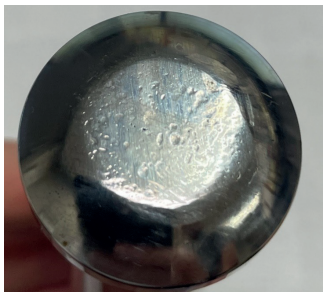
Michal Luleczka and Michal Baczek, NATOLI ENGINEERING

INTRODUCTION

Proper care of components in a tablet press is a critical aspect of the tablet manufacturing process. As a key element in producing solid oral dosage forms, the tablet press is pivotal in forming tablets. We'll explore the basic understanding of wear components for a tablet press. covering simple steps to keep it working efficiently and producing quality tablets.

PRESSURE ROLLS

Monitoring the condition of pressure rolls in a tablet press is crucial for maintaining the overall efficiency, quality, and safety of the tableting process.
Any damage such as pitting, denting, or discoloration on the face is considered rolling fatigue, generally related to excessive pressure, lack of or improper lubrication, or contaminated lubrication. Damage on the surface of the pressure roll will eventually transfer and cause damage to the punch heads.

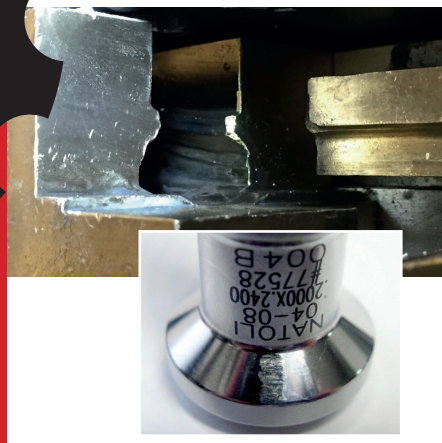


TOP: Fig 1 - Damage on pressure roll
ABOVE: Fig 2 - Head damage transfered from pressure roll

Pressure rolls should be examined for "run-out" or concentricity. Use a dial indicator securely attached to a magnetic base. Manually rotate the roll while resting the indicator tip against its surface. The resulting measurement should be taken to assess whether the wear on the pressure roll falls within the acceptable tolerance range. The acceptable run out for pressure rolls typically is 0.05 mm (.002") T.I.R. (total indicator read-out), an out-of-round pressure roll will affect the consistency of tablet hardness and thickness.

CAM WEAR

Cams play a pivotal role in ensuring the synchronised and precise vertical movement of punches. Monitoring cam condition to identify excessive wear, as worn cams can lead to tablet contamination, improper synchronisation of the tableting process, premature punch wear, and contribute to certain tablet defects.



ABOVE:
Fig 3 - Excessively worn fill cam
INSET: Fig 4 - Related head punch damage

Fill cams are responsible for the depth of fill, which determines the formulation volume in the die cavity before dosing. A worn cam can cause inadequate fill, which will directly impact the weight and hardness of the tablet.

ABOVE: Fig 5 - Worn ejection cam
INSET: Fig 6 - Severe ejection cam wear
BELOW: Fig 7 - Worn die pockets from improper installation

EJECTION CAMS

Ejection cams are responsible for ejecting the tablets from the die cavity. They control the vertical movement of the lower punch during the ejection phase of the tableting cycle.

Worn ejection cams can reduce the height setting of the lower punch for proper tablet ejection, causing tablet take-off-related damage, such as chipping, capping, shearing, etc. An excessively worn ejection cam can increase wear on the lower punch head.

DIE POCKET WEAR

Improper die installation can cause premature wear leading to enlargement of the top section of the die pocket. Typical wear created by improper die installation and not using the correct set-up tools and procedures is indicated in red, in figure 7.

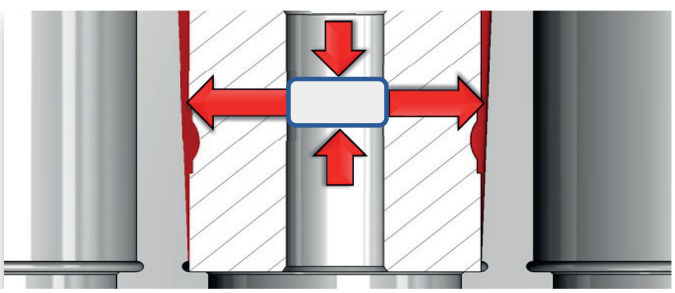
Die pocket wear, as shown in Figure 9, will allow the die to be forced out of centre when torqued into position by the die lock. When the die bore and upper punch tip are not aligned, it will exacerbate the wear on the upper punch tips and lead to various issues, such as tip failure, tablet capping, and/or lamination.

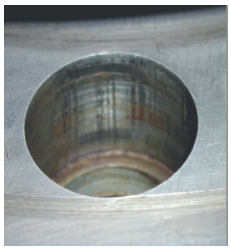
An oversized die pocket does not offer support to the die during compression as the compression forces and can initiate cracking which will be first identified on the top of the die, as depicted by the vertical arrow in figure 10.

Fretting is often observed at the top of the die and results from die pocket wear. Fretting is a term used for discoloration and damage appearing as rust. It is due to the high-frequency cyclic motion due to excessive clearance of mating parts as the dies expand and contract during compression.

DIE LOCK SCREWS

The overall condition of the die lock screws is directly responsible for properly securing the dies. Cleanliness of the threads of the die lock screw and the mating threads in the turret are critical to provide proper torque. Using a pre-set, non-adjustable torque wrench is recommended. Over-tightening can cause excessive stress and damage to the dies and die lock screws. Under-tightening will not secure the dies adequately, which can allow the die to rotate, losing the die to punch tip alignment. It can also allow the die to rise above the die table, causing extensive damage to the





ABOVE: Fig 9 - Worn/damaged die pocket
ABOVE RIGHT: Fig 10 - Fretted and cracked dies
RIGHT: Fig 11 - Damaged die lock screw with contaminated threads

powder feeder. Die lock screws must be replaced when worn or damaged. Figure 11.

FEEDER INSTALLATION

The feeder installation in a tablet press delivers a controlled and uniform formulation flow into the dies for compression. Consistency of powder flow is essential for achieving uniform tablet specifications. Improper feeder setup can lead to excessive powder loss and variations in the compression process. Contact between the feeder and the die table will cause premature wear of the die table and feeder. This wear is recognised as grooves on both surfaces and can lead to metallic contamination of the tablets.

PUNCH GUIDES AND KEYWAYS

Premature wear of punch guides and keyways in a tablet press can lead to a range of operational issues and affect the overall performance of the tablet press.

Prevalent reasons for this:

- Lack of proper lubrication between the punch and the punch guide and keyway can increase friction, wear, and binding.
- Excessive formulation or other contaminants entering the punch guides and keyways will reduce the lubrication effectiveness and can cause abrasion and accelerated wear.
- Keyway damage due to misaligned cams.
- Avoid causing dings, dents, or burrs at the edges of the punch guide and keyways when installing punches.
- Improper handling and set-up procedures can lead to unnecessary damage and wear.

ABOVE: Fig 12 - Damaged keyway

CONCLUSION

It's not if, it's when worn parts must be replaced. Press components discussed in this article should be monitored and replaced when needed. An understanding of tablet press wear parts is paramount to keep the press operating at optimum performance. Tablet manufacturers should maintain an inventory of replacement parts and components to minimise operational downtime.

Introducing New Equipment into GMP Facilities: *A VENDOR'S PERSPECTIVE*

Richard Hammond, Chief Technical Officer, Sphere Fluidics

Introducing new equipment in life sciences typically follows a well-worn path. At first, as a vendor, your new device is picked up by the research community as it enables new experimental approaches or provides new measurement methods. The barriers to entry are relatively low at this point: fundamentally, you need a moderately reliable product that is safe to use. Over time, the technology becomes more familiar, its benefits are clear, papers start to emerge, and a community of users begins to develop. The applications then start to move away from pure research and your device becomes an integral part of drug development processes. In this evolution, the product may be recognised for its potential within manufacturing workflows. Whilst an exciting next step in the technology's breadth of applications, this introduces new regulatory hurdles. Suddenly, the acronym 'GMP' is everywhere and life is getting much more complicated.

It is important to consider the key challenges in successfully making this shift from research vendor into a Good Manufacturing Practice, or GMP-ready vendor, and the critical areas to prioritise to ensure a seamless transition into this new world. It requires a step-change in maturity of processes, documentation and rigour but with long-lasting benefit to develop high-quality devices more quickly and efficiently.

At the heart of GMP is a straightforward premise: all drug products sold on the market should be consistently safe and effective from the first batch to the last, and controlling the manufacturing processes is key to achieving this. This underlying principle then extends to become a range of directives, regulations, and guidelines built over many years as the science and technology used for manufacture develops.

As an equipment vendor, the most important concept to grasp is that GMP does not apply directly to you. It applies to the organisation manufacturing and marketing the drug product – your customer. The second most important concept is that GMP is serious. Failure to comply with the various regulations and guidelines has a significant impact, ultimately including the shutting down of facilities and the product being taken off the market. Hence achieving and maintaining GMP compliance is business-critical for your customers and you need to play your part in this. You can't achieve compliance for your customer, but you can undermine your customer's compliance – and they won't be happy if you do.

In a European context, the overarching legislation controlling medicinal products for human use encompasses a number of Directives and Regulations published as EudraLex Volume 1 'EU pharmaceutical legislation for medicinal products for human use'. There are then several Guidelines to support the basic legislation – in particular EudraLex Volume 4 'Guidelines for good manufacturing practices for medicinal products for human and veterinary use'. The core of Volume 4 is Part 1 – Basic Requirements. These nine chapters encompass the full extent of GMP and are well worth reading to get an insight into what your customers need to do. However, from an equipment vendor perspective there are a number of critical areas to focus on.

Risk management: The biggest change in transitioning from research equipment vendor to GMP equipment vendor is embracing risk management. The systematic assessment of product quality risk to drive decision making and continuous improvement is a cornerstone of quality management within GMP, as it is recognised as an efficient and effective approach. Within the context of new equipment, the ICH Guideline 9, referenced in Volume 4, makes specific mention that 'The application of quality risk management to the design, validation and technology transfer of advanced production processes and analytical methods, advanced data analysis methods and computerised systems is important'.

This change needs to impact your entire organisation. Risk

> Suddenly, the acronym 'GMP' is everywhere and life is getting much more complicated.

management processes need to be applied to equipment design, testing, manufacture, and customer support. This lets you identify and understand the risks to product quality, take appropriate, prioritised actions to manage the risks, and communicate this clearly to your customer via good record keeping.

Demonstrating fitness for purpose – qualification and validation: Another big change from research to GMP is the substantial level of evidence required to demonstrate the equipment and processes are capable of doing the job they need to do. There are two parts to this: qualification and validation. The first focuses on the equipment itself: "does it meet specification and perform as intended?" The second focuses on the process performed by the equipment, facility and operators: "can the process make the product to the necessary quality?"

Typically, as an equipment vendor, qualification is the dominant area of work with validation conducted by your customer with your support. Qualification includes six well-defined stages starting with a defined User Requirements Specification (clearly stating what the equipment needs to do) through to Performance Qualification (robust evidence the equipment can achieve the necessary performance). Working through all these can take significant time and effort but the customer will expect it and want to be closely involved, so they can be confident your device is fit for purpose and the necessary evidence is recorded.

Computerised systems: Almost all equipment today includes some form of computerised system – software running on hardware to fulfil certain functions. Such systems have their own guidelines within Volume 4 as they present a unique set of challenges in maintaining quality and performance. Again, a risk management approach is mandated throughout the system lifecycle, particularly to decide the extent of validation and data integrity controls required. User Requirement Specifications are needed to describe the function of the system and these need to be traced through the system life cycle – providing evidence the requirements are met whenever the system is used.

Electronic signatures are allowed, but these must be permanently linked to the respective record with time and date. This then leads to a plethora of requirements about user access to systems and managing data integrity so records cannot be altered. This is a good example of an area where moving into GMP requires a lot more rigour in specifying and validating software to demonstrate compliance with guidelines than a research device.

Change control: The final big area of change is change control. Here, research and GMP are diametrically opposed in their goals. Research is all about trying new things and making new discoveries; GMP is all about maintaining product quality and managing risk. This needs a change in mindset for the equipment supplier. As a research equipment vendor, rapid updates and providing new ways of doing things are expected. Maintaining this approach will cause your GMP customer a huge headache.

Any change to your device, hardware or software, needs to be thoroughly planned, assessed for risk, and appropriate re-qualification and re-validation performed to show no impact on quality. This then has a knock-on effect for your customer regarding their user training, update of operating procedures, and other validation activities. As a vendor, you need to understand this and implement robust change control and communication processes with your customers.

Making the transition from research equipment vendor to GMP-ready vendor requires changes in how you run your business and interact with your customers. These changes are both practical and conceptual – changing the mindset of your team to understand the challenges a GMP-compliant customer faces. However, the benefits are substantial for both parties: new technology and equipment embedded in drug manufacture, advancing healthcare and helping patients.

> User Requirement Specifications are needed to describe the function of the system and these need to be traced through the system life cycle

LONZA Q&A:

Typically, Q&A's are focused on a single topic or a single individual. To keep things interesting, here at EPM HQ, we devised a range of questions to put towards a varied group of subject matter experts at Lonza. Here's what they had to say...

Author: **Jai McIntosh**

Jai: Lonza state that they're focused on "supporting clinical trials from pre-clinical through to Phase III and launch". What are the key challenges to overcome when building the pathway from pre-clinical trials to product launch?

Jakob Bonde, Head of Regulatory Affairs, Small Molecules: The key challenge is obtaining sufficient manufacturing process knowledge to deliver the phase-appropriate clinical and commercial drug quality while only manufacturing sufficient material to complete the activity at each clinical step including development activities for subsequent steps. Mindful that customers wish to invest in development activities increasing the chances of a commercial approval, and not a stock of material. Such activities might be investing in manufacturing optimisation for increased yield while obtaining an understanding of potential and observed process impurities, and how to purge observed impurities including carrying out fate and purge studies with synthesised impurities, if required. Understanding method validation requirements at each step is also paramount while investing.

Determining the best time point to introduce manufacturing process changes such as optimisations for scale-up for global rollout could also be a hurdle particularly if the applicant has decided to present very detailed CMC information to the health authorities.

Jai: Antibody Drug Conjugates (ADCs) have widespread potential yet require specific facilities and expertise to successfully develop. How do Lonza avoid protein aggregation and unstable linkers?

Charles Johnson, Senior Director, Commercial Development: First, looking at protein aggregation, it's important to state that different proteins naturally have disparate aggregation potentials, which are determined by complex compositional and structural characteristics. The antibodies used to make ADCs are generally less prone to aggregation as long as they are kept away from the isoelectric point where they have no net charge. This can be important during conjugation with the payload, where pH can be a consideration.

A more significant issue with ADC aggregation is the nature of the payload and the drug-antibody ratio (DAR). Many ADC payloads are hydrophobic, and this can promote ADC aggregation through payload-payload interactions. This can even cause the ADC to precipitate. The effect can be exacerbated by a high DAR. Careful linker design can be used to avoid this, as introducing hydrophilic components such as PEG units or groups like sulfonates that ionise at physiological pH can help. The HydraSpace sulfonamide linkers developed by Synaffix, now part of Lonza, are a good example, as they offer the potential for more efficient conjugation, better stability, and an improved therapeutic index.

Turning to unstable linkers, early generation ADCs that relied on conjugation chemistry could lose their payload over time under physiological conditions, with disulfides and non-ring-opened maleimides both susceptible to drug exchange with human serum albumin. The result was loss of efficacy and increased off-target toxicities. Improvements in conjugation chemistry, such as using ring-opened maleimides or shifting to more stable click chemistry, have helped. This includes the Synaffix GlycoConnect technology, which uses metal-free bioorthogonal click chemistry, and its proprietary bicyclo[6.1.0]nonyne (BCN) compound.

Overall, though, careful process development work is important for avoiding problems such as aggregation. There is great benefit in addressing these issues early on, and this is why we have a toolbox of technologies to support bioconjugate design from the outset.

Jai: How are the safety issues of developing Highly Potent Active Pharmaceutical Ingredients managed and to what extent are HPAPIs becoming increasingly significant in the drug development pipeline?

Guixian Hu, Head Development Services Small Molecules Visp and Nansha: HPAPIs are of increasing importance within the drug development pipeline. Ever more molecules entering it are now being deemed highly potent, with a CAGR of about 10% for HPAPIs, compared to 6% for those with more normal potency. Highly potent compounds are also an essential component of antibody-drug conjugates. A

significant reason for the sector growth is the rising proportion of the development pipeline that comprises oncology indications, where high potency is even more likely; roughly a third of small molecule drugs in development now are for cancer indications.

Ensuring safety is a particularly important consideration when manufacturing an HPAPI, as such small quantities are required to have a therapeutic effect. Of course, containment is important, to protect both the operators in the plant and the wider environment around the facility as well as prevent cross contamination between different products if multi-purpose assets are utilised. Equipment is available to ensure both primary and secondary containment throughout. This includes options for solids charging, liner ports used for sampling procedures, and endless liner systems for unloading.

Effective, validated procedures are essential for cleaning down the equipment after use – and rigorous testing to ensure that potential carryover from one product to the next is controlled down to the accepted level. Facility design, operating procedures, well trained personnel and personal protective equipment all play a part in keeping every employee and patient safe.

Jai: What are the benefits of improving API dissolution rates?

Deanna Mudie, Sr. Principal Engineer R&D: For APIs where oral absorption is limited by the dissolution rate – in other words, the API's dissolution in GI fluids is the slowest step to the drug appearing in the bloodstream – increasing the dissolution rate can increase the rate and/or extent of absorption of drug in the bloodstream.

Increasing the rate of absorption of drugs in the bloodstream can often result in a higher maximum concentration in the bloodstream, and it can also be achieved more quickly. Both of these are desirable for a drug requiring a rapid onset of action. Also, increasing the extent of absorption can also lead to a greater amount of drug reaching the bloodstream. This increased exposure can maximise the drug's therapeutic effect.

Even if a drug is not dissolution-rate limited under typical administration (such as in healthy volunteers in the fasting state), it can become so when given under different conditions, such as in the fed state, when co-administered with gastric acid pH reducers, or in geriatric or paediatric populations. This may lead to a decreased rate or extent of absorption under these conditions, which can result in a food label or special dosing instructions being required. Therefore, increasing the dissolution rate, even under typical administration conditions, may allow these issues to be avoided.

Jai: Lonza operates a Micronisation Centre of Excellence in Monteggio, Switzerland. What are the key targets of this centre and what methods are used to achieve this?

Salvatore Mercuri, Head of MSAT, Monteggio: The Monteggio Micronisation Centre of Excellence is a key component of our particle size reduction offering. One of the tools in the toolbox for improving an API's solubility, and therefore its bioavailability, is to make smaller particles, as the increased surface area is one way to increase the dissolution rate. It is also important for inhaled dosages, where size and consistency of particles is critical for successful delivery to the deep lung.

Importantly, at Monteggio, as well as standard APIs, we have the necessary equipment and containment in place to work with highly potent molecules and controlled substances. And we have the apparatus required to scale up the process up to 100x. We have specialist equipment, too. Notable examples include the ability to carry out cryogenic milling, and also opposite jet milling. This includes a new JS100 opposite jet mill designed and made in house that will facilitate the development of high-performance particle engineering solutions that are directly scalable up to our existing JS300 jet mill for production.

“Facility design, operating procedures, well trained personnel and personal protective equipment all play a part in keeping every employee and patient safe.

HOW WILL AI-POWERED BIOPROCESSING BRING US CLOSER TO THE ERA OF *Personalised* Medicine?

JUAN GARZÓN, CEO OF CULTZYME

Despite being individually uncommon, rare diseases collectively affect a large number of people. In fact, 1 in 17 people will be affected by a rare disease at some point in their lives. Diagnosis of a rare disease can leave a patient hopeless due to the lack of treatment available. Personalised medicines hold huge potential to improve the lives of patients with rare diseases, as well as improving the efficacy of treatments for more common diseases. However, their production is expensive and challenging, and advanced technology will need to be applied to support this emerging field.

PROGRESS SO FAR

The first personalised medicine made and administered to a single patient was milasen. In under a year, neurologist Timothy Yu developed an antisense oligonucleotide designed solely for Mila Makove. Administered in 2017, the drug helped to halt the progression of Mila's condition, Batten disease, and improved her quality of life over the next four years. However, Mila's disease was already in the advanced stage when she received the drug, and she unfortunately died in 2021.

The development of milasen was a major milestone in the advancement of personalised medicines and provided a glimmer of hope to the millions of people in the world with rare genetic diseases. However, to become more widely available, the price of personalised medicines needs to come down. For this to happen, drug manufacturers need to develop processes that enable them to produce small batches of medicine quickly.

Traditional biopharmaceutical manufacturing is based on volume production. Producing significant volumes of product at a large, centralised facility is generally much more economical than small batches. This presents a problem for personalised medicines, in which only small quantities are required that are produced close to the individual patient. Moreover, the production equipment needs to be flexible enough to manufacture multiple different medicines for different patients.

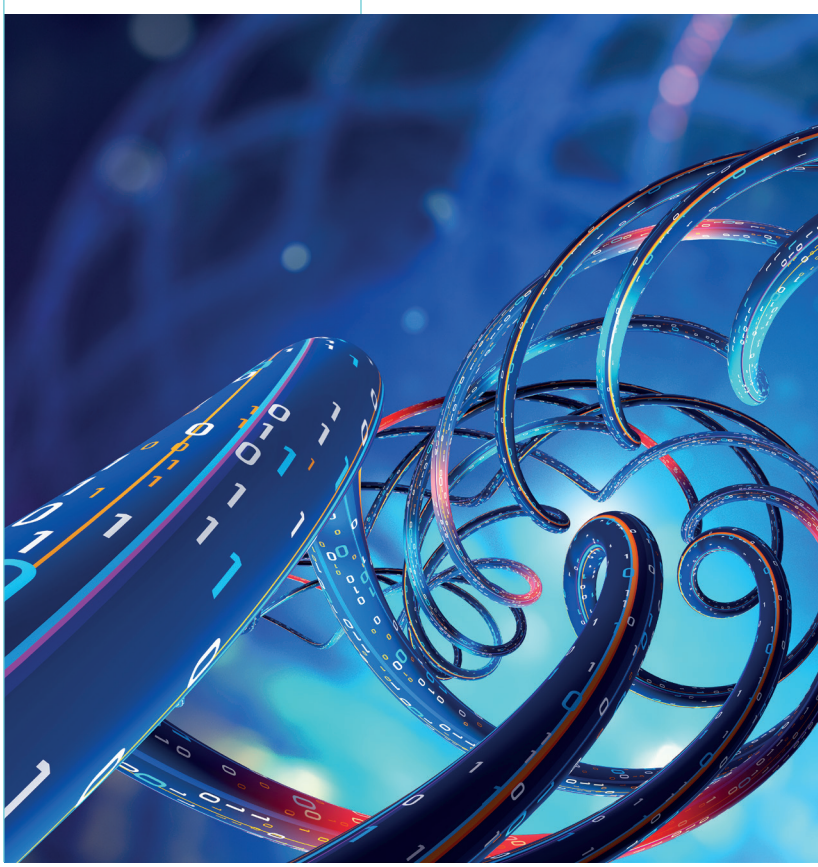
> **Integrating AI and quantum-inspired algorithms offers a way to overcome these challenges and make benchtop bioreactors a more effective system to produce personalised medicines.**

A SMALL-SCALE SOLUTION

Benchtop bioreactors are useful devices for small scale biopharmaceutical manufacturing, being portable with a small footprint. Simple bioreactors consist of a sterile vessel and a magnetic stirrer to provide homogeneous mixing of the culture medium and cells. These devices are suitable for small scale cell and bacterial cultures. However, for more advanced applications, such as personalised medicines, more sophisticated features are needed.

Advanced bioreactors include features such as temperature, pH and agitation controllers, as well as dissolved oxygen and carbon dioxide monitors. A particularly sophisticated feature is a continuous flow system, in which fresh culture medium is continually added and spent medium is removed by peristaltic pumps, thus maintaining a constant cell density and improving metabolite production.

In addition, miniaturised benchtop bioreactors have been developed for high-



speed, high-throughput testing. These devices use very small culture volumes and allow for multiple simultaneous tests, making them ideal for screening microorganisms or developing new cell lines.

BIOREACTOR CHALLENGES

The bioreactor market has been greatly lacking in the capacity to control and monitor critical process parameters in real time, which hinders early detection of problems and optimisation of culture conditions. In addition, the devices can be complex to operate, thus requiring skilled operators for their use. This poses a problem to smaller companies with limited specialised personnel and is exacerbated by the shortage of talented individuals with digital skills in the biopharma industry.

Other issues include a lack of guarantees regarding sterilisation. Traditional methods, such as autoclaving, require high operability and do not prevent recontamination once the bioreactor tank has been removed from the autoclave. In addition, many benchtop bioreactors require a high initial investment, as well as high operating and maintenance costs. Benchtop bioreactors can be bulky and not very scalable, meaning that the results obtained on a small scale do not necessarily translate into a larger scale process.

Another spanner in the works is that once the device has been purchased, it can require continuous calibration of the sensors, constant replacement of parts and rigorous training for operators. In addition, many current bioreactors require manual data collection, which is time-consuming and error prone. If the data collection is automated, it is often limited to only a few sensors, which can result in loss of vital information that can affect accuracy of analysis and replication.

AI IS CHANGING THE GAME

Integrating AI and quantum-inspired algorithms offers a way to overcome these challenges and make benchtop bioreactors a more effective system to produce personalised medicines. AI allows the management and analysis of large amounts of data, as well as elimination of repetitive manual tasks through process automation. Operational and logistical costs are reduced, and quality of results is increased, as AI enables greater control over the bioreactor. Temperature, pH and agitation can all be precisely controlled, and the system can continually learn to improve performance.

AI can also reduce the number of experimental designs needed to obtain a minimum viable product, enable in vitro modelling and optimisation, and facilitate the scalability of bioprocesses. If a digital twin is implemented, all process data can be collected and stored in the cloud in real time, ensuring accurate replication and possible early detection of problems. With data stored in the cloud, AI opens up the possibility to control the biofabrication process from anywhere in the world, improving efficiency and flexibility.

Peristaltic pumps can be replaced with nanofibre-based delivery systems where the different substrates such as nutrients, microorganisms and cells, are stored. This reduces the risk of contamination and means the substrates can be automatically dosed as part of the AI system.

The promise of personalised medicines offers hope to millions of people with rare genetic diseases. However, in order for personalised medicines to become more widely available, biopharmaceutical manufacturers must develop processes that can manufacture small batches of medicines quickly. AI-powered benchtop bioreactors enable more efficient, scalable and affordable manufacture of bespoke treatments — bringing us closer to the era of personalised medicines.

“AI can also reduce the number of experimental designs needed to obtain a minimum viable product, enable in vitro modelling and optimisation, and facilitate the scalability of bioprocesses.

SGD PHARMA:
An Interview With *Olivier Rousseau*

Author: **Jai McIntosh**

SGD Pharma has been a leader in the moulded glass packaging market for a significant number of years. Central to their vision and plan is a persistent striving for excellence that runs through the company from top to bottom. To better understand the company and their plans for the future, we at EPM HQ sat down with Olivier Rousseau, CEO of SGD Pharma, for a quick discussion...

Jai: Can you outline the strategy for SGD Pharma?
Olivier: Our vision is to become the global market leader in primary pharmaceutical glass packaging, not just for moulded glass which we currently are. Put simply, we want to significantly grow the size of the company at a consistent and sustainable rate. We plan on improving our performance, by ensuring we continue our processes striving towards commercial excellence and operational excellence - excellence is central to our business philosophy. In the pharma industry, quality and service needs to be at the highest possible standard. We try to do everything possible to provide the right product at the highest quality, whilst ensuring we manage our customers to an outstanding level. We do this with a long-term goal of building strong relationships predicated on quality. For me, and for the company, striving for excellence year-on-year is the main goal.

We will also develop adjacent businesses and continue to provide high levels of quality and service to our customers, this involves continuous investment into improvement. This year we announced our joint venture with Corning to produce tubes to help us further grow our continuing business. We hope to continue forming partnerships that will support our growth and ability to provide innovative and game-changing solutions to our customers.

Jai: In which markets do you see the most potential for growth?
Olivier: We will defend, grow and consolidate our position on moulded as well as supporting the growth of tubular vials on a global scope. There is also room for growth in cosmetic and beauty packaging which we currently manufacture at our Zhanjiang plant in China. We have extended our ranges available globally, introducing sampler sizes to take advantage of the market opportunity for glass packaging in cosmetics packaging with the embrace of green and reusable values.

Jai: How have your sustainability and CSR goals impacted your company strategy?
Olivier: ESG is at the heart of our strategy. One of our key priorities is decarbonisation and we intend to lead the glass pharma industry with our decarbonisation efforts. We have set ourselves the goal of reducing CO2 emissions from 2020 by 35% in 2030 (Scope 1 and 2) and by 65% in 2040 (compared with 2020 baseline: scope 1 & 2) - these public commitments are one of the ways we are showing that, at the core of what we do, is maintaining excellence whilst adapting to the needs of the planet. We are also dedicated to improving our facilities and the health and safety of our sites so that we can minimise any potential risk of accidents and improve the working environment for our employees.

Four of our plants, including Saint-Quentin-Lamotte which is our global centre of excellence, are already certified with ISO 50001 & no 15001 for the design, implementation and maintenance of an energy management system. We also have a number of projects to reduce our carbon footprint and water consumption across all geographies. In January 2023 we were awarded a gold EcoVadis rating in recognition of our sustainability efforts. SGD Pharma is also in the top 1% of companies rated by EcoVadis in the manufacture of glass and

glass products for sustainable procurement and in the top 2% for labour and human rights. This leading position outlines our intentions to ensure a sustainable transition within our industry.

SGD Pharma is SBTI committed and currently working on 1,5°C scenario decarbonation pathway validation including our scope 3 emissions.

Jai: After a difficult few years of rising energy and material costs due to external global factors, how do you plan to minimise or prevent further cost increases being passed onto customers?

Olivier: We have a very clear energy hedging strategy, and as a consequence of that we have a clear visibility of our future energy costs. We will continue to be transparent with customers about our energy costs and present the benefits of our energy hedging strategy. Unfortunately, this was not sufficient to cover all cost increases given the high inflation that was experienced. We will also continue preserving energy at our manufacturing sites.

SGD Pharma secured its supply of energy by being considered a priority manufacturer by local governments and by implementing initiatives to reduce our plants' dependency on natural gas and electricity. We also have a strong network of partner suppliers with long term contracts in place meaning that we have security of raw materials. To avoid further cost increases and demand of supply impacting our business, we have taken a few steps to accelerate the optimisation of energy and raw materials at our sites. This includes increasing efficiency of production and leveraging historic data from our ERP system to forecast usage. The increasing CAPEX investment into reduction of our plants' carbon footprint is more urgent in light of needing to ensure production costs are minimised for the benefit of our customers.

Jai: What actions have you taken to keep high-quality production going at your global manufacturing sites?

Olivier: We have already made significant investment at our sites to fit state-of-the art glass manufacturing equipment, with our SQLM plant in France being a centre of excellence for moulded glass. Additionally, in Vemula, India, we have invested into a new tubing facility to expand pharmaceutical manufacturing in India and allow us to adopt Corning's Velocity Vial technology platform which will help pharma companies respond to increasingly complex capacity and quality issues while meeting global demand for critical medicines. We broke ground on the €60M site in June and expect Velocity Vial production to begin in Q1 2024.

We also will continue our high standards of quality control, as I have mentioned, a constant pursuit of excellence is key to us as a company. We will continue to innovate and develop our offerings to ensure that our customers have exceptional quality glass packaging.

> **In the pharma industry, quality and service needs to be at the highest possible standard. We try to do everything possible to provide the right product at the highest quality, whilst ensuring we manage our partnerships to an outstanding level.**

HOW TECHNOLOGY IS REDEFINING *Pharmacovigilance Studies*

MATT WILSON, CEO, uMed

uMed CEO Matt Wilson highlights where and how technology is transforming pharmacovigilance (PV) and the developments on the horizon that will help to drive more proactive and efficient safety monitoring.

THE ROLE OF TECHNOLOGY IN REDEFINING PHARMACOVIGILANCE STUDIES

We are in the midst of a technological revolution where every corner of the healthcare industry buzzes with excitement about the potential of big data, artificial intelligence (AI) and machine learning. But with such rapid progress, it can be hard to keep pace and make sense of what these advancements mean in practice and where the real value is.

PV, which revolves around the collection and analysis of large volumes of information about medicines use, stands to benefit enormously from the resource and efficiency savings offered by technological advancements. This is particularly true in the realm of post authorisation safety studies (PASS) where pharmaceutical companies are looking to elucidate the risk profile of a medicine long-term, in real world settings. Advances in technology are helping PV teams to improve information gathering on adverse drug reactions (ADR) by increasing the breadth and quality of data available and facilitating closer contact with patients.

PROCESSING AND ACCESSING DATA

As more sources of health information are opened up, new technologies are simultaneously increasing our capability to manage the increasing volumes of data now available. Speed and efficiency are the greatest advantages here. Enhanced processing power means we can now run complex searches, through large volumes of data, in shorter times, using fewer people. This is a particular advantage in labour intensive areas of signal detection such as literature review.

AI and machine learning have also given us the ability to search for patterns in these large data sources. Analyses and recommendations are delivered much faster, near instantaneously in many cases, allowing us to predict the likelihood of ADRs and become more proactive in how we mitigate and manage risk.

EHR OUTREACH

Setting up and maintaining a PASS is notoriously expensive and

resource intensive, however, integration of EHRs into electronic data capture systems is driving improvements in cost, efficacy and scalability.

For example, one notable pain-point has always been the difficulty in re-engaging with patients to verify individual case study reports (ICSRs) against the four criteria (identifiable patient, identifiable reporter, suspect drug and adverse event). Traditionally this involves an unreliable approach of passing a request through a physician, to contact a patient, to provide the missing information. Integrating EHRs can streamline and increase the accuracy of this process, giving PV teams access to contact details that allow them to go directly to pre-consented patients to collect missing information.

EHR-driven outreach is also helping to eliminate bias in PASS to recruit more representative patient populations. High quality, robust data is essential and bias at the start of a study means results will be flawed throughout. Bias can creep in through numerous avenues including physician influence, geography and type of healthcare centre. It's impossible to limit completely but interrogating EHR data at the outset of a study is helping PV teams target and essentially over recruit in the groups that are underrepresented to create a better balance.

CONNECTING WITH PATIENTS

Mobile technology has been a game changer within healthcare, making everyone much better connected and facilitating the growth of decentralised studies, apps and portals that allow patients to engage in research remotely.

As well as making participation more convenient by reducing the number of routine clinic visits, mobile tech is driving improvements in data accuracy in PASS. Information can be recorded instantaneously and with patients able to report from home, holiday, the office or wherever they have access to their mobile device, there are fewer gaps in reporting. To support this further, reminders to check-in can be added to electronic calendars and in-app prompts and notifications can be sent.

DATA SECURITY CONCERNS

Strong data security and ethical oversight must underpin technology use. Health data is among the most sensitive information we hold and its use must be approached with a deep concern for patient data safety and with the appropriate accreditations and safeguards in place such as HIPAA compliance (for US), ISO27001 and 9001:2015.

Building trust with physicians and patients is essential and both should expect explicit information and absolute transparency about how their data will be used and the level of identification risk to allay any concerns and provide reassurance.

Data anonymisation carries the lowest level of re-identification risk. Original information that can identify the patient is deleted and therefore not subject to GDPR. Whilst this might be more reassuring for the patient, it removes the ability to follow-up any reported safety signals. As a result, pseudonymised data is often the preferred option for PASS. Identifiable information is replaced with a code or pseudonym to allow reidentification of patients if required. As there is some level of identification risk, suitable mitigation measures must be in place and GDPR adhered to.

A NEW ERA FOR PV STUDIES

Technology is continuously evolving and will bring further opportunities to improve PV practices and medicines safety. There are several key trends to keep an eye on that will impact the future:

AI in data analytics: As our understanding of how to use AI and algorithms to interrogate data evolves, we'll be able to take a more prospective approach in PASS, rapidly detecting and predicting adverse events rather than having to rely on retrospective analyses.

AI driven case processing: Automatic categorisation and processing of ICSRs will reduce manual work and streamline current systems, giving PV teams more time to focus on complex cases and risk assessment.

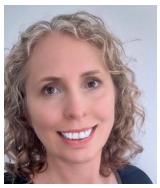
Wearables and remote tech: Tech companies are flocking to the medical space, recognising the potential to track and provide data for health and fitness enthusiasts and the life sciences industry. This will bring more data and more questions. Fast and easy access to patients will be essential to check and supplement information about ADRs to increase accuracy and ensure robust data.

Data integration and interoperability: Regulatory authorities are already looking into harmonising healthcare data across borders and health systems. This will be a giant leap forward, reducing the vast amount of time and money it takes to combine and format incompatible data from different sources and providers to unravel and capture ADRs.

In conclusion, the ongoing technological revolution represents a new era for PV studies, with the power of AI and greater connectivity enhancing our ability to detect, assess, understand and prevent adverse effects and any other medicine-related problems. The potential for even more significant progress in PV practices and medicine safety is on the horizon, but we'll only keep pace with these advances by maintaining patient trust and keeping a sharp focus on protecting their privacy.

> **Flexibility and bespoke approaches are key, and it's vital that development processes are tailored to fit molecules.**

BUILDING INTEGRATED AND FLEXIBLE APPROACHES FOR RAPID DEVELOPMENT OF NEW MOLECULAR FORMATS



Alice Harrison, Global Technical & CMC Director (Analytics) and **Stuart Jamieson,** Global Technical & CMC Director (Downstream Development) at Lonza

EVOLUTION OF THE DNA TO IND PATHWAY

In the last decade, the path from identifying a novel molecular target to submitting an investigational new drug (IND) application has evolved.

Driven by greater demand to develop biological therapeutics quickly, companies have adapted to patient and market needs, harnessing integrated approaches to move swiftly, accounting for cost, time, and new technologies. Innovative solutions have emerged as mammalian cell culture derived molecular formats have become increasingly diverse, often encompassing multiple chains and varied protein domains, presenting unique challenges during development and manufacture.

The success during COVID-19 to rapidly deliver vaccines has given industry renewed confidence to evolve development and manufacturing. This has led to greater emphasis on an integrated, tailorable approach in developing new molecular format therapeutics, moving towards innovation and effective risk management.

Increasing acceptance of pooled cell culture supernatant as representative of clonal material, and increased acceptance of risk, has enabled some activities to be brought forward, including analytical method establishment, purification development and formulation development. Cell pool use now allows such activities to happen in parallel to producing a lead clonal cell line, significantly reducing timelines. Formerly complex procedures, like developing monoclonal antibodies, have become routine. This enables CDMOs to

leverage platform and toolbox approaches for more complex molecule development. Automation has increased, alongside upfront 'de-risking' strategies, which increase overall likelihood of a new biological therapeutic succeeding and obtaining regulatory approval.

NAVIGATING THE NEW ERA

Amidst new-found innovation, biopharma companies value the ability to adjust and prioritise aspects of their programmes to suit product requirements.

At Lonza, our capabilities span the full development pathway, from confirmation of an optimal molecular candidate to delivery of the complete IND package. Working collaboratively with our customers, we see two common development pathways emerging: a rapid full-service scope, due to a desire to reach the clinic at speed, and a bespoke approach, due to customer in-house capabilities, development status or progress milestones. When working with customers at various development stages, it's critical that CDMOs facilitate entry at any point in a products development lifecycle, providing flexibility whether early candidate de-risking is required, a lead candidate has been selected, or further milestones have been reached - such as the availability of the clonal cell line.

In such a landscape, a clear, adaptable development strategy is vital. Integrated approaches and an advanced toolbox of capabilities can ensure the rapid development of new molecular formats.

THE NEED FOR FLEXIBLE, BESPOKE PROGRAMMES

CDMOs can provide expertise and access to many services alongside a clear CMC strategy, providing certainty for customers. Primarily, this comes from bespoke solutions and flexible means to support new molecular types, in which accelerated timelines can be provided even though the molecules themselves are diverse, have unknown characteristics and behave less predictably from the start.

We know drug development can strain resources, drain budgets, and consume time. In a fiercely competitive landscape, bespoke solutions and individually designed programmes are essential. One approach at Lonza is to shape our programmes to sync with a molecule's profile and company. Recently, we launched four accelerated gene to IND programmes: monoclonal antibody, bispecific antibody, scaffolds and recombinant proteins, and Fabs and Fusions. These programmes provide integrated, accelerated starting points for each molecule, fully adaptable and flexible to the customer's needs.

If a customer wants to speed up the path to the clinic, they can choose an integrated drug substance and product programme to suit their molecule type. If they want to be more cautious, we can support building a stepwise CMC strategy, reviewing it after each key milestone to assess any product liabilities and provide data for funding and technical decisions.
It's through this type of intelligent, technically driven management that solutions can be found for each case.

THE IMPORTANCE OF TAILORING

Flexibility and bespoke approaches are key, and it's vital that development processes are tailored to fit molecules. The goal is to isolate a clonal cell line, delivering high titers and desired product characteristics, which can be manufactured easily at the intended IND scale and support further scale-up and commercial operations.

Choosing a CDMO with extensive knowledge of platform, toolbox and bespoke solutions allows tailored strategies that meet the unique requirements of complex molecules. For example, in purification development, a platform protein A resin may be suitable for initial purification of a bispecific heterodimeric IgG antibody, but presence of product specific impurities may require a high throughput screening solution to develop intermediate and final polishing purification stages. Similarly, a recombinant protein product, with no antibody Fc region and no-platform resin available, will require a purification strategy screening, a toolbox of appropriate capture resins, in addition to the development of further purification stages.

CDMOs rely on experience, established methods, cutting-edge technologies and analytics to reduce clone selection, process development, scale-up and production risks. One automated technology that we've used for selecting monoclonal or bispecific antibody-expressing cell lines allows us to monitor thousands of cells for productivity, growth and clonality. The best performing lines are taken for further evaluation in automated bioreactor systems, enabling robust scale-up. If additional optimisation is required, small scale DoE studies can be performed in miniature bioreactors to adapt the process parameters.

This highlights the importance of tailoring. Using methods to fit molecules and programmes, companies can work with commercially viable, high producing cell lines to compete in crowded markets.

PROVIDING TECHNICAL SUPPORT AND OVERSIGHT

To support a timely delivery process, it's important to embed critical development milestones, and utilise technical risk management through continued support and oversight.

It's important to use a data driven approach by using phase and molecule appropriate analytical methods. These are established early on, by selecting from an extensive toolbox of available methods, evaluating molecule specific performance, and developing where required to support testing and release.

Data review at key points within predefined technical stage gates enables the proactive identification, and mitigation, of risks.
The above strategies are supported by drug substance and drug product specialists, who facilitate required course adjustments or risk mitigations to keep the programme on track. These experts have the in-depth CMC knowledge to deliver each project and support the generation of a proposal for development and GMP production.

AN EMPHASIS ON SPEED

Drug developers must navigate evolving market conditions and post-pandemic pressures.

The speed of early manufacturing and time taken to move from drug identification to approvals are critical factors. The funding that drug developers receive is closely linked to hitting these milestones. This may mean that the sooner a product's viability is proven, the quicker additional funding can be secured.

Whilst demand and time pressures are building, so are innovations. Improvements in automation, high throughput process screening and analytics, mean that not only timeline reductions are possible for mammalian derived biologics, but additional knowledge and data is collected during initial development.

By choosing a well-established and optimised cell line development platform (including optimal vector design, gene integration strategy, cell lines, media and feeds) and a toolbox of purification and analytical approaches, development timelines can be accelerated, and overall costs reduced.

Early Cryopreservation as a Stepping Stone to

SUSTAINABLE CELL AND GENE THERAPY MANUFACTURING

Priya Baraniak, Ph.D, Chief Business Officer and **Dominic Mancini,** VP Operations, OrganaBio

Scalability and sustainability have become choke points for cell and gene therapy (CGT) manufacturing, hindering efforts to improve accessibility to these novel life-saving medicines. Many developers are wrestling with logistics in their efforts to overcome limitations linked to cost, development time, product quality, and patient waits. For both autologous and allogeneic cell-based therapies, the way starting material is shipped has sparked a significant debate around if and when to transition from fresh to cryopreserved cellular materials. The field is also exploring new advances that would give the makers of CGTs even more flexibility in their cold chain.

Fresh leukopaks are often preferred for the presumed advantages in cell counts or functionality. International Society for Cell & Gene Therapy (ISCT) President Jacques Galipeau has said, "Mesenchymal stem cells are like sushi: fresh is best," and this remains the prevailing wisdom for other cell types as well. But this preference must be reconciled with the reality that for every approved chimeric antigen receptor (CAR)-T therapy today, cryopreservation of patient apheresis materials is a critical intermediate step for shipping to the manufacturing site.

The reluctance to move to cryopreserved starting materials is, in part, because therapeutics developers have not completed sufficient comparability work to conclusively demonstrate the difference in therapeutic outcomes when using fresh versus frozen materials. However, even when fresh materials are shown to be superior, it is all about trade-offs. Fresh materials come with a host of challenges, like marrying donor collection scheduling to manufacturing availability, variability in cell yield and composition, and frequent delays in transportation. When materials aren't frozen, and the clock is ticking, even minor delays or temperature excursions can result in degradation, potentially rendering materials unsuitable for further manufacturing. In addition, when manufacturing slots are missed, significant costs are incurred in materials, reagents and personnel, not to mention GMP suite fees if a developer is working with a contract development and manufacturing organisation (CDMO).

MOVING TO CRYOPRESERVATION

Cryopreservation, on the other hand, eases many of these pain points. Materials are carefully preserved at extremely low temperatures, allowing for longer-term storage to enable more flexible timelines. The field is rife with stories of trials – and patients – endangered by logistics failures. Even leading third-party logistics services don't typically own their own jets, and some developers have resorted to chartering private planes for transportation of clinical apheresis material to mitigate risk to clinical manufacturing. These stopgap solutions are not scalable nor suitable for commercial manufacturing, and they render the therapeutics cost-prohibitive to most people. To democratise cell-based therapies, costs associated with the manufacturing of these drugs must be minimised.

The logistics of CGT manufacturing must account for issues like scheduling, which is uniquely complex for allogeneic therapies. Developers must undertake an often-painstaking search for just a few ideal healthy donors who will supply all the material for early clinical trials. Once they find an individual who meets their needs, developers who rely on fresh materials find themselves at the mercy of a donor's day-to-day life. These are not employees, but volunteers whose ability to donate on a regular schedule can be impacted by a variety of unpredictable life events such as illness, childcare and work schedules.

In the case of autologous therapies, patients must often travel far to reach a clinical site or hospital where their material can be collected. In many cases, the patient's health may be so compromised that they are unable to travel. In addition, something as innocuous as a flight delay may snarl collection scheduling and manufacturing. Through cryopreservation, developers and their supply chain partners can give patients and donors flexibility in their appointments and ensure availability doesn't bring

manufacturing to a halt.

Utilising cryopreservation is also likely to reduce barriers to patient access. It can drive down total development costs, which can impact the ultimate price to payers. But just as important, it enables the easier delivery of living therapies to rural areas and underdeveloped countries. Most people don't live near an esteemed cancer centre, like MD Anderson or Memorial Sloan-Kettering, and manufacturing at scale today relies on centralised hubs. If you live far away from a suitable treatment centre, the odds of getting a therapy dependent on fresh starting materials shrinks drastically.

STARTING THE TRANSITION EARLY

To mitigate the hurdles and costs associated with transitioning from fresh to cryopreserved materials, the transition should ideally begin early in the discovery process – in general, the earlier the better. When a therapy needs to be transitioned to a cryopreservation process during clinical development, it necessitates extensive comparability studies and potential modifications to the Investigational New Drug (IND) application, or a new application all together.

Frozen cellular materials are more expensive to make, including state-of-the-art formulation media and freezing in controlled rate freezing equipment, and are typically shipped in expensive liquid nitrogen systems. As a result, it may be tempting to rely on fresh materials early on when developing a new therapy. The significant downstream costs of commercialising a therapy reliant on fresh materials are rarely considered during early stages of development. Although using frozen materials presents a higher upfront cost, the overall cost of the program is less than when using fresh materials.

If the final drug product quality is inadequate when starting with frozen materials, it would be better to find out quickly and adapt the processes or, if necessary, fail sooner and allow developers to pivot before costs spiral.

There are a variety of approaches for performing comparability studies to enable the transition to frozen, typically including a combination of fresh and frozen materials from the same patient or donor, allowing researchers to mitigate the impact of donor-to-donor variability.

GROUNDWORK FOR FUTURE ADVANCES

While cryopreservation has become the standard for preserving commercial CGT materials, technologies in development today have the potential to expand access even further. Some cells deteriorate with cryopreservation, reducing cell viability and functionality. This is a particular problem for natural killer (NK) cell therapies, which do not recover well in the days post-thaw. Here, companies are pursuing relatively new biopreservation media which protect cells and extend shelf-life at refrigerated or ambient temperatures.

Additional work in lyophilisation, or freeze-drying, could help circumvent the challenges associated with maintaining a cold chain, potentially revolutionising the global access to CGT therapies. Many drugs today are lyophilised, an innovative solution that allows shelf stability of biological materials at the range of ambient temperatures. The United States Department of Defense has invested in lyophilisation research with the aim of developing methods to preserve blood-based products for rapid deployment in the battlefield where typical cold chain options are not practical.

Application of lyophilisation in the biopharma CGT space could help democratise access to these therapies across the world, but technical challenges remain steep. Cells and tissues are mostly water, and drying them out typically has devastating consequences. However, extracellular vesicles like exosomes are simpler and can be lyophilised more easily than cells. Similarly, lipid nanoparticles can be readily lyophilised and have tremendous application both as vaccines and as critical reagents to these more advanced cellular therapies.

STRATEGIC PARTNERSHIPS: THE KEY TO SUCCESS

As the CGT field progresses, developers need consistent access to high-quality research- and clinical-grade materials. Companies that provide cellular starting materials, with established supply chains and expertise in donor recruitment, tissue collection and cell isolation, play a pivotal role in ensuring a steady and dependable source of materials, transported in whichever state best suits a developer's needs.

These partners are critical and can assist in developing a well-thought-out strategy to transition from fresh to cryopreserved materials. They can also provide guidance on critical process parameters (CPPs) and critical quality attributes (CQAs), helping with chemistry, manufacturing and controls (CMC) planning in advance of regulatory engagement. When it comes to cryopreservation, regulatory agencies are primarily concerned with safety. An experienced supply chain partner will ensure cryopreservation media used to formulate starting materials are GMP-ready and registered with the Food and Drug Administration (FDA), or other pertinent regulatory agency.

Through improvements in cryopreservation, and innovations on the horizon like biopreservation and lyophilisation, the CGT industry is on the path to overcoming the cold-chain challenge and making a more significant impact on healthcare worldwide. By starting the transition early and collaborating with reputable providers of cellular starting materials, developers can position themselves to ensure a robust supply of these critical starting materials and development of a sustainable and scalable manufacturing process. Ultimately, the goal is to make these therapies accessible to all, regardless of geographical location or logistical constraints.

“Additional work in lyophilisation, or freeze-drying, could help circumvent the challenges associated with maintaining a cold chain, potentially revolutionising the global access to CGT therapies.

THE *COMPLEXITIES* OF MANUFACTURING

Orphan Drugs in Product Development

Cornell Stamoran, Vice President, Strategy and Government Affairs, and **Matt Mollan,** Vice President Operations, Catalent

There are approximately 1,500 active pipeline compounds within orphan designation today, and, like the overall pharmaceutical pipeline, small molecules make up the majority of these. Since 2010, 44% of all FDA New Molecular Entity / Biologics License Application approvals, and 67% of all new cancer treatments have been orphan drugs, however, there remains a real patient need for more, as 90% of rare diseases currently have no FDA-approved treatment.

For developers, the Chemistry, Manufacturing and Controls (CMC) challenges for orphan drugs are very similar to other products: incorporating patient factors in early decision making; appropriate formulation development; and selecting the optimal dosage form. However, for manufacturing, the key issues presented by orphan drugs are the high costs, the limited commercial capability for low volume products, and ensuring product consistency during scale up. There must be fit-for-purpose manufacturing and supporting infrastructure to efficiently and successfully scale up and deliver products for patients.

There are two major pressures on orphan drug programmes: time and the availability of the API drug product – every gram of product is precious. Due to challenges like limited bioavailability and the need for targeted release profiles, small molecule oral products are becoming more complex to deliver. Given the constraints of time and resources, it's crucial to optimise formulation and dosage form design to enhance the likelihood of success.

CHALLENGES OF FORMULATION AND PROCESSING

For development, a risk-based CMC plan is strongly recommended, and this should be shared and discussed with regulators ahead of time and throughout the development process. Where possible, predictive tools should be used to minimise API usage, with the goal being to lock in the process as early as possible.

Time pressure means that whatever formulation is used in first-in-human trials is almost certain to become the one that remains through to commercial launch. Formulation needs to be developed using excipients that are transferable to larger scale processing, and once the formulation is fixed at registration, then processing is the key to commercial success. Figure 1 shows the orphan drug pipeline by dosage form, and it is evident that oral tablets and capsules are by far the most favoured by pharma companies. Oral tablets and capsules are a widely used dosage form due to their convenience, versatility, and cost-effectiveness. These advantages make them a preferred choice not only for pharma companies

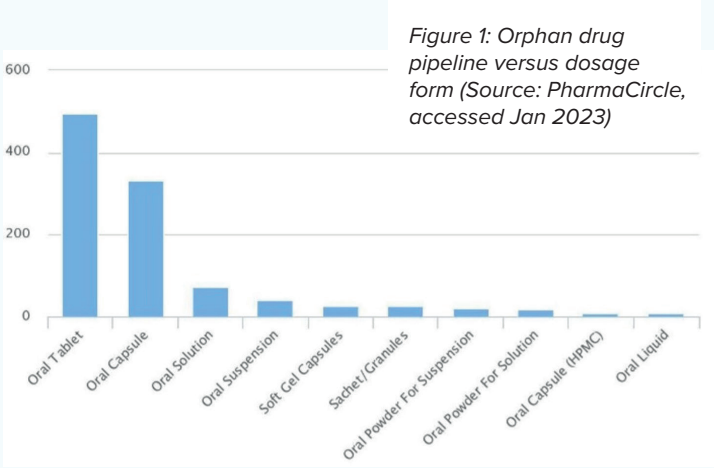


Figure 1: Orphan drug pipeline versus dosage form (Source: PharmaCircle, accessed Jan 2023)

but also for numerous patients and healthcare providers. By selecting the appropriate formulation technology, it becomes possible to orally deliver many drugs that would otherwise be difficult or impossible to administer.

SCALE CHALLENGES

Unlike other drug programmes, orphan drugs are unlikely to scale up to traditional, commercial batch size manufacturing, and often, the product will be launched at what would be considered clinical scale.

It is inefficient to be continually making batches of drug products during clinical development, so a choice must be made as to whether to scale up to a level to gain understanding of the process, providing product for all investigations and studies. Choosing an optimal batch size is not easy, as there will be limited batches per year manufactured when a drug is commercialised, but the scale must be balanced against stability data to align with the determined shelf life. Making too much may lead to waste, but too little could lead to supply disruption. However, it is unwise to scale to a situation where only one or two batches are manufactured per year, because should anything unexpected happen during manufacture, this could incur a huge loss.

Scaling up activities can be done post-approval, and there are less resource pressures once the product is generating sales, however, any manufacturing should be carried out on fill / tableting lines and equipment that is already approved. Pre-launch, available API material is extremely precious, so using a site and equipment that has already been through regulatory approval with different products can de-risk the CMC process and avoid global regulatory queries, which could otherwise cause delay and additional costs.

As products will be distributed around the world, it is best practice to use materials that are globally acceptable and meet all countries' regulations from the outset. This will prevent any issues if a new country is added to a clinical trial, where there are different standards than others, such as for bovine versus non-bovine capsules, as well as different colourants and dyes.

TIME CHALLENGES AND PARTNERING FOR SUCCESS

Orphan drug programmes typically shorten the time to market by 3-8 years through expedited approval pathways when compared to traditional drug development paths. For innovators, this means there may be a reduced amount of real time stability data for commercial material, and initial commercial supplies may need to be provided by a clinical manufacturing facility, should the chosen commercial facility be unavailable.

In the last 10 years, on average, 55% of orphans approved from all company types, approved by the FDA, were outsourced from a finished dose form standpoint. Finding a commercial drug product manufacturing partner that can work all the way through from development to commercial scale keeps the process simple, by reducing the number of tech transfers and the process familiarisation phases of each hand off.

To minimise risks, it's important to have a CDMO partner with experience in manufacturing orphan designated products at a small scale and limited batch. It is beneficial that they have a strong regulatory inspection history with global regulatory authorities and have produced NDA-approved products in the last three years so that they are aware of the current expectations and regulatory compliance.

Closely integrating clinical trial logistics with product supply can save time and money, while reducing transition points such as in manufacturing, packaging, clinical supply and analytical support, where possible, along with a strong project management foundation, is key to successful projects in the orphan area.

CONCLUSION

In summary, when developing orphan drugs, companies need to take certain key measures into consideration. One of the most important steps is to create a risk-based CMC plan, which will help to identify and mitigate potential risks early on. Another crucial aspect is to use predictive tools that can minimise the usage of API, which will conserve resources and speed up the development process. Choosing an optimal batch size for orphan drugs is a delicate balancing act between ensuring a stable supply and minimising waste, while also considering the need for a scalable formulation. Additionally, partnering with a CDMO that has experience in manufacturing orphan drugs can reduce the risk of errors and delays. Finally, it is essential to closely integrate clinical trial logistics with product supply, which will save time and money and ensure that patients have access to the drug as quickly as possible.

> **Due to challenges like limited bioavailability and the need for targeted release profiles, small molecule oral products are becoming more complex to deliver.**

Talking points

Medicann - Ireland's First Medicinal Cannabis Clinic

Ireland is set to get its first medicinal cannabis clinic, covering all therapy areas, since it became legalised in June 2019.

Medicann, the award winning medicinal cannabis clinic is launching the first clinic in Ireland, and are now accepting patients who wish to know if they are eligible for treatment. The new clinic covers all conditions treatable with medicinal cannabis, and not just those recognised by the Medical Cannabis Access Programme in Ireland.

Through a virtual appointment, via our secure tele-health portal we can establish if you are eligible to be prescribed medicinal cannabis which comes in various forms flowers, oils and topical creams to help patients. With an experienced team of local specialist consultants, Medicann's first clinic opened in 2019.

Gary Whipp, CEO of Medicann Ireland said: "When medicinal cannabis first became legalised in the UK back in 2018, early on I saw the potential it had to improve the quality of life for patients and we have been providing access to this natural medication for patients that are eligible for the last 4 years.

As the first clinic to launch in Ireland, we know patients have been waiting for local access to this medication, and we are very much looking forward to helping patients manage their condition better, and improve their quality of life under the guidance and help of our specialist Doctors here at Medicann."

Research shows that medicinal cannabis may be helpful for treating a variety of conditions including chronic pain, mental health and female conditions such as endometriosis. It is also prescribed to patients suffering from multiple sclerosis, and may help to alleviate symptoms such as sleep problems, improving spasticity and alleviating pain.

In Ireland, there are currently more than 9,000 people diagnosed with MS, and through the government's Medicinal Cannabis Access Programme, qualifying patients can apply for funding to cover the cost of medicinal cannabis. This first clinic will play a vital role in presenting the efficacy of cannabinoids to the UK and Ireland pharma market, perhaps more importantly, to those who legislate.

Cannabinoids are likely to cement their position as a significant medical substance throughout 2024.

UK GOVERNMENT INVEST £100M IN AI FOR LIFE SCIENCES

A new mission announced by Rishi Sunak will accelerate the use of AI in life sciences to tackle the biggest health challenges of our generation. In a recent speech, the Prime Minister announced that a £100 million in new government investment will be targeted towards areas where rapid deployment of AI has the greatest potential to create transformational breakthroughs in treatments for previously incurable diseases. The AI Life Sciences Accelerator Mission will capitalise on the UK's unique strengths in secure health data and cutting-edge AI.

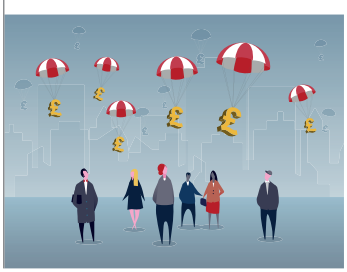
The £100 million will help drive forward this work by exploring how AI could address these conditions, which have some of the highest mortality and morbidity.

For example, AI could further the development of novel precision treatments for dementia. This new government funding for AI will help us harness the UK's world-class health data to quickly identify those at risk of dementia and related conditions, ensure that the right patients are taking part in the right trials at the right time to develop new treatments effectively, and give us better data on how well new therapies work. By using the power of AI to support the growing pipeline of new dementia therapies, we will ensure the best and most promising treatments are selected to go forwards, and that patients receive the right treatments that work best for them.

AI driven technologies are showing remarkable promise in being able to diagnose, and potentially treat, mental ill health. For example, leading companies are already using conversational AI that supports people with mental health challenges and guides them through proactive prevention routines, escalating cases to human therapists when needed – all of which reduces the strain on NHS waiting lists.

Rishi Sunak said: "AI can help us solve some of the greatest social challenges of our time. AI could help find novel dementia treatments or develop vaccines for cancer. That's why we're investing a further £100 million to accelerate the use of AI on the most transformational breakthroughs in treatments for previously incurable diseases."

This funding will help us to invest in parts of the UK where the clinical needs are greatest to test and trial new technologies within the next 18 months. Over the next 5 years, we will transform mental health research through developing world-class data infrastructure to improve the lives of those living with mental health conditions.



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