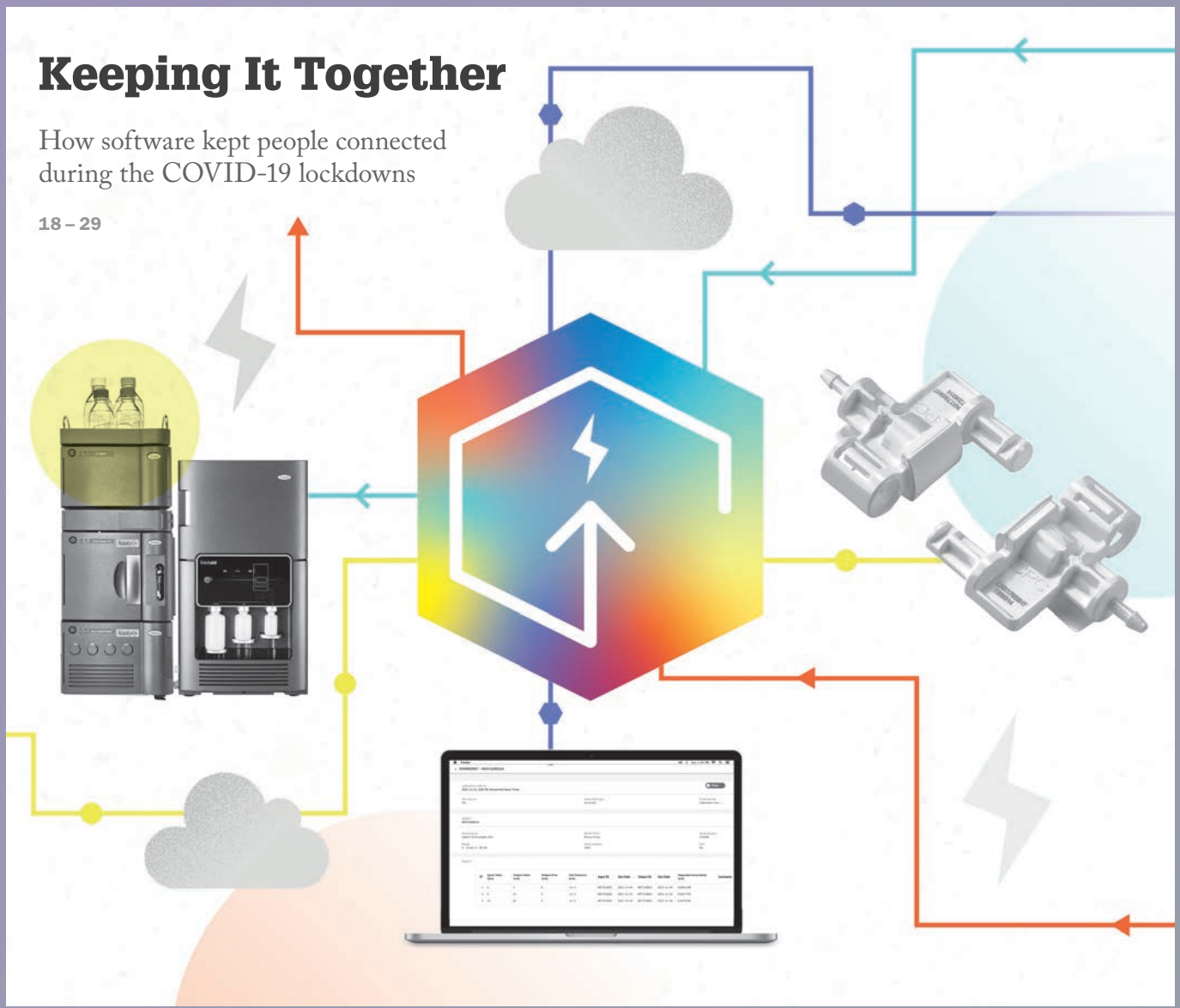
SEPTEMBER / OCTOBER 2022 # 87

the Medicine Maker®

Keeping It Together

How software kept people connected during the COVID-19 lockdowns



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Every Disease Has Its Day

Is now finally the time for Alzheimer's drug development to shine?

In all my years of writing about the industry, failures in Alzheimer's clinical trials have been an unfortunate constant. And then, in 2021, the FDA approved Biogen and Eisai's anti-amyloid antibody Aduhelm. Seemingly good news – but the move was not welcomed by all, with many stakeholders questioning the drug's efficacy (1). Medicare refused to offer coverage unless patients were taking the drug as part of a clinical trial, and an investigation is ongoing into how the drug was approved in the first place given limited evidence of efficacy. In May 2022, Biogen announced that it would "substantially eliminate the commercial infrastructure" for Aduhelm – and also noted that CEO Michel Vounatsos would step down (2).

Undeterred, the companies are back in the spotlight with another attempt to tackle the intractable. In October 2022, Eisai and Biogen released data from a phase III trial of lecanemab – another anti-amyloid mAb (3). Primary and key secondary endpoints of the trial were met, with data showing that the drug appears to slow cognitive decline by 27 percent in people with mild Alzheimer's disease. The US Alzheimer's Association responded (4), "These are the most encouraging results in clinical trials treating the underlying causes of Alzheimer's to date."

Whereas Aduhelm ignited controversy, the industry seems cautiously optimistic about lecanemab. However, the drug has not yet reached the approval stage – brace yourself for more discussions if and when this happens. For now, both companies are enjoying surging stock prices.

Eisai will present more detailed data at the Clinical Trials on Alzheimer's Congress in late November and plans to publish the results in a peer-reviewed journal. Eisai will also take the lead on the regulatory submission for the drug.

Dealing with the harsh realities of old age is inevitable for most of us – but the onset of Alzheimer's (and other forms of dementia) in family members or friends is a particularly frightening prospect. I look forward to hearing what experts think of the full results.

Stephanie Sutton
Editor

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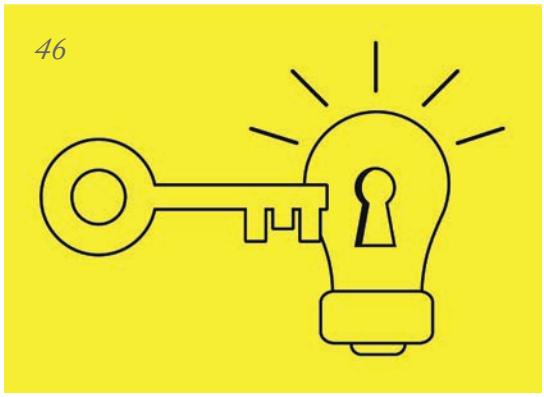

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How we keep connected in the age of remote working

the Medicine Maker

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Credit: Major Tom Agency / unsplash.com

From Viral Video to Magic Medicine

In 2014, the Ice Bucket Challenge raised millions; eight years on, we have a new FDA-approved therapy

Before completing its ongoing phase III trial, Amylyx Pharma's AMX0035 combination therapy for amyotrophic lateral sclerosis (ALS) has received approval from the FDA (1). The drug will be marketed as Relyvrio. Believe it or not, the roots of its success lie in the viral ALS Ice Bucket Challenge.

Unless you are a very young reader (welcome!) or locked yourself away from all forms of media in 2014, you'll remember the Ice Bucket Challenge. To take part, the challenger would receive a bucket of ice cold water over the head before challenging a friend or colleague, with participants and challengers donating money to charity and/or urging others to do the same or join the Challenge.

Just as the trend was achieving liftoff, ALS activists Pat Quinn and Pete Frates launched the more specific ALS Ice Bucket Challenge – a move that captured the moment, eventually raising over $220 million in donations for ALS research worldwide in 2014. The funding was certainly boosted thanks to celebrity participants that included Justin Timberlake, Homer Simpson, pre-presidential Donald Trump, and cult film director David Lynch (who, perhaps ahead of his time, nominated Vladimir Putin).

The lion's share of money raised by the Challenge went to America's ALS Association. In June 2016, the Association committed $750,000 of this money to fund a pilot clinical trial of AMX0035, a combination therapy for ALS. The Association then gave $1.46 million to the Northeast ALS Consortium to fund a phase II trial of AMX0035.

The Association kept on pushing in 2020, securing more than 50,000 signatures to call on the FDA to approve AMX0035. In 2021, they kept the pressure up, holding discussions with the FDA and a special "We Can't Wait" meeting, where people with ALS spoke directly to the regulators.

In the phase II trial that preceded the approval, the drug was found to slow the loss of physical function in people with ALS and potentially extend their survival. These positive results – combined with the fact that Amylyx has chosen to keep the price below the most recently FDA-approved ALS treatment – appear to suggest that all those buckets of ice-cold water might just pay off for patients.

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Pfizer Scrutinizer

EU auditors chase people involved in a COVID-19 vaccine deal

A major investigation is underway within the halls of EU bureaucracy concerning allegations of impropriety by EU officials in their acquisition of COVID-19 vaccines via a 1.8 billion dose deal with Pfizer (1). Digging by the European Court of Auditors found that the deal did not go through a joint negotiation team, and now investigators are seeking to verify whether the deal was made via as-yet undisclosed texts with none other than Albert Bourla, Pifzer's CEO (2). Bourla was lined up to testify before the EU's COVID-19 committee but pulled out and had a company executive speak on his behalf – but the European Parliament has made it clear that they still want a word with him (3).

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IMAGE OF THE MONTH

Factory On Film

Fujifilm Diosynth Biotechnologies employees at the opening ceremony of the new large-scale microbial manufacturing facility located at its Billingham, UK campus.

Credit: FUJIFILM Diosynth Biotechnologies

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QUOTE of the month

"While we've made great progress, the virus is still with us."

Pfizer CEO Albert Bourla commenting publicly upon catching COVID-19 for the second time in two months

the Medicine Maker POWER LIST

The 2023 Power List Is Open for Nominations

From CEOs to scientists, from engineers to experts... tell us who inspires you!

Nominations are officially open for The Medicine Maker 2023 Power List! The List will celebrate gifted individuals at the forefront of innovation in biopharmaceuticals, advanced therapies, and traditional small molecule therapeutics, with ten experts included in each of the three categories.

We welcome nominations from all corners of the industry for people involved in the development or manufacture of drugs. Consider: whose hard work should be recognized? Who is revolutionizing the field? Who is disrupting the status quo?

This goes beyond corporate CEOs and directors; you can nominate drug discoverers, process engineers, clinical trial experts, regulators – anyone making a mark on the industry. You can even nominate yourself!

So, which medicine makers will you pick? Tell us here: tmm.txp.to/powerlist-nom-2023 Nominations close on February 3, 2023 and the final list will be published in April.

From Arctic Fish to New Cell Therapy Preservation Technologies

Cryopreservation should maintain the function and viability of organs and cell therapies, but the process is riddled with challenges. Can nature-inspired proteins make a difference?

Credit: Jeremy Bishop / unsplash.com

Cryopreservation was first brought to life in the 1950s when researchers discovered the preservatory properties of glycol. Since then, cryopreservation methods have been refined and redefined to improve their ability to maintain the quality and functionality of cells and organs. However, there are still challenges.

According to Xiaoxi Wei, CEO and Co-Founder at X-Therma, the low temperatures and freezing agents involved can introduce the risk of crystal formation in tissues, which ultimately leads to cellular damage. "To minimize the impact of ice formation, companies rely on cryoprotectants," she says. "But current techniques are significantly limited by the poor performance of cryoprotective agents (CPAs). Regardless of the freezing method (e.g., slow-freezing or vitrification), a CPA or combination of CPAs is needed."

But CPA reliance isn't without its problems. The toxicity of these agents – notably dimethyl sulfoxide (DMSO), one of the most common – can have consequences for patients. Wei says, "DMSO is toxic to cells at high concentrations and is also known to cause adverse reactions, such as vomiting and arrhythmia, in patients receiving DMSO-preserved stem cell therapies. Typical DMSO concentrations are around 10 percent; cell or bone marrow transplants containing 30–60 percent DMSO are associated with at least one side effect or complication."

Inspired by nature, X-Therma has developed a biomimetic molecule that enables scientists to store cells and organs at sub-zero temperatures while avoiding potential changes to functionality and viability. "We created a biomimetic molecule of a naturally occurring antifreeze protein found in Arctic fish species," explains Wei. "This novel molecule – a bioinspired peptoid – provides a scalable, nontoxic, DMSO- and serum-free cryopreservation solution that can be used for organ and tissue storage."

The biomimetic molecule prevents recrystallization by controlling the process of annealing, the physical changes that occur as a result of temperature changes. This prevents the formation of small ice crystals and "improves the post-thaw viability" of tissues and organs. These properties, according to Wei, also make the nature-inspired peptide suitable for storing cell therapies because it can maintain their quality and be used in tissue/cell banking. Wei says, "In manufacturing gene and cell therapies, many manufacturers face scalability issues, toxicity, and proteomic and epigenetic changes from DMSO that reduce the effectiveness of the therapy. Better biopreservation methods are crucial to evolve the regenerative medicine market and underlie the sourcing of cellular material and the manufacture, storage, and delivery of all regenerative medicines."

Wei and her colleagues are also exploring other applications of their platform technology. She says, "We all heard about the complicated process of maintaining cold temperatures for extended transport during the COVID-19 pandemic. Vaccines could very well be another area in which this technology offers value."

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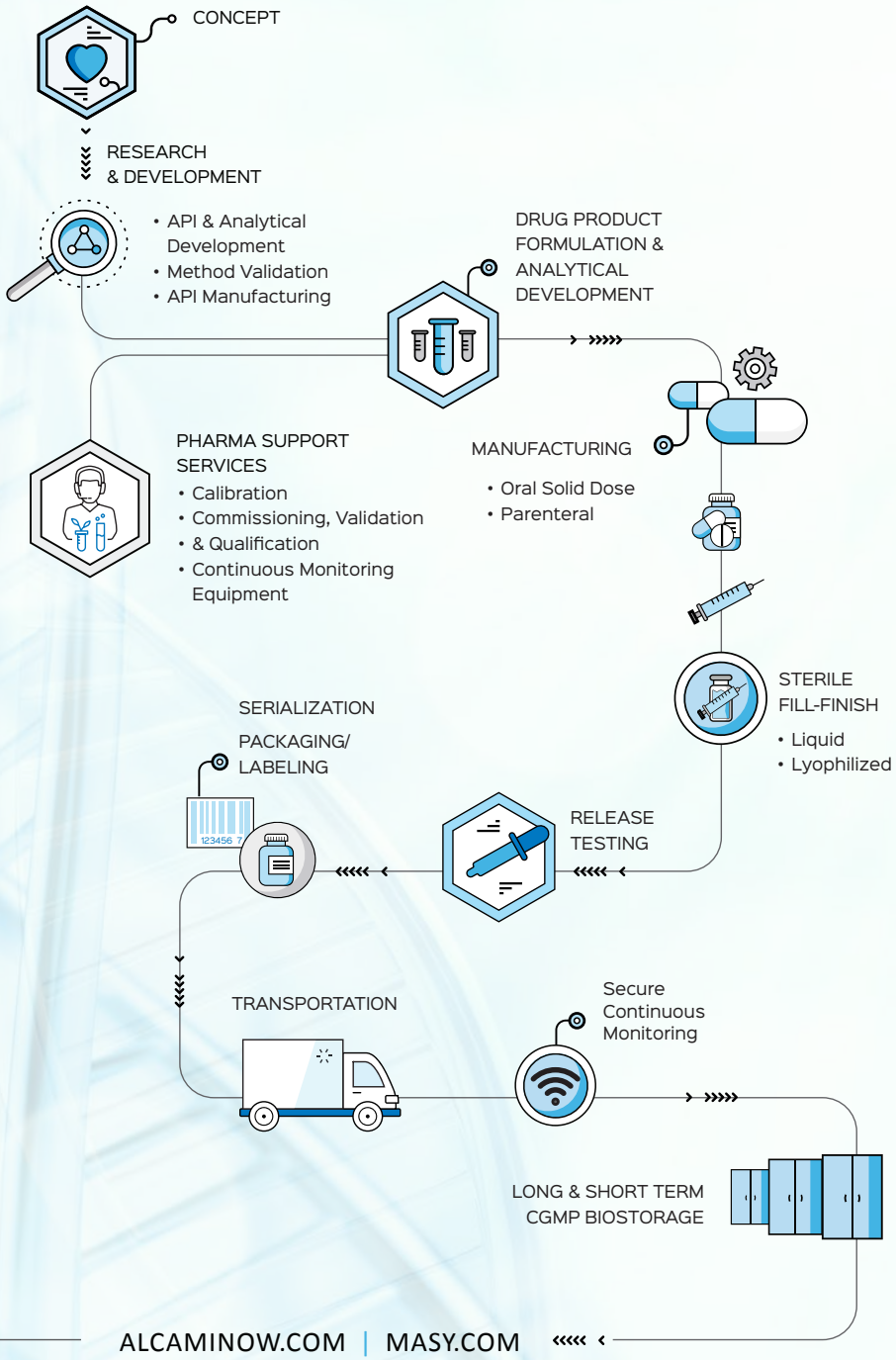

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The Dual Sourcing Approach

How robust is your strategy? Are you prepared for supply chain interruption? In today's turbulent world, risk mitigation strategies are a must – and having a secondary supplier in place for the manufacturing and packaging of life-saving critical medicines is no longer a 'nice to have'. It should be an essential part of your strategy in terms of patient health.

By Shawn Cain (Senior VP Development & Manufacturing), Rebecca Coutts (General Manager Tredegar), Rob Jones (Executive Business Development Director), and Kate Smith (Director of Quality) at PCI Pharma Services

Whether they know it or not, patients are heavily reliant on complex supply chains for sometimes life-saving medications – and that's why good supply chain management has always been important for the industry, particularly in the case of critical medicines. However, the COVID-19 pandemic, natural disasters, the war in Ukraine, disruption in labor through staff shortages, and other events in recent years have emphasized how vulnerable the industry's supply chains truly are and underlined the crucial importance of robust risk mitigation strategies. In addition, the threat of disruption in the supply of equipment, components, and materials – including raw materials – is also a significant risk.

PCI Pharma Services is a leading global Contract Development and Manufacturing Organization (CDMO) providing integrated development, manufacturing and packaging solutions on behalf of clients. Since the start of the pandemic, hardly a conversation or review meeting with our clients has gone by without some aspect of the supply chain being discussed. In fact, conversations are now delving deeper into supply chains than ever before, with clients asking what else they can do to mitigate risk and ensure continuity of supply of life-changing therapies to their patients. The FDA has also accelerated such discussions by releasing draft guidance "Risk Management Plans to Mitigate the Potential for Drug Shortages, May 2022" for the industry on the need to have robust risk management plans to mitigate the potential for drug shortages. In short, risk mitigation is now at the top of the industry's priorities.

Reading the ripples

At PCI, we always work in partnership with our customers to minimize the impact of any supply chain disruptions, ensuring vital supplies are available to patients when needed, whether that be for clinical or commercial supply. Part of our risk mitigation approach is to continually analyze supply chain ripples to predict potential waves – or even tsunamis – of disruption. Though it's true that black swan events present challenges in terms of prediction and preparation, a good risk mitigation strategy should take into account worst-case scenarios. In other situations, such as Brexit, where there is time to prepare; we developed a robust "Brexit plan" to ensure our UK and EU operations, supply chains and ultimately supply of therapies for patients were not affected, but not all companies are so proactive.

However, it doesn't always take a significant world event to create supply chain disruption. New guidelines and updated regulatory documents are a fact of life in the pharma industry – and suppliers who fail to keep on top of changing legislative and regulatory requirements can create ripples in supply chains that affect many others. In Europe, an update to Annex 1 on sterile manufacturing was just released. Companies now need to adjust to the new requirements to ensure there will not be disruption in the supply chain as a result

Good risk mitigation should proactively seek to understand the drug product and its entire supply chain, identify and prioritize the potential risks, and develop preventive or corrective action plans to minimize supply disruption – especially when it comes to life-sustaining and life-supporting products.

Two suppliers are better than one

Before the pandemic, supply chain simplification was considered a key trend, with some companies preferring single-source supply partners. That said, some astute companies were already establishing two sources of drug substance and drug product supply because of the value in potential risk mitigation; after all, a second source of supply can add greater flexibility and capacity should there be a sudden change in demand – or an unforeseen challenge that affects the primary supplier. These companies found themselves in a better position to navigate the supply chain disruption created by the biggest and most unprecedented black swan event in recent memory, and were able to switch on their second source supply and maintain supply to patients.

As companies take on board lessons from the pandemic, dual sourcing is fast gaining traction as a key strategy for critical medicines. Importantly, some companies are seeking additional geographic coverage using suppliers across different regions to meet local drug product market needs, a strategy which both reduces disruption but also their carbon footprint, which in turn has a positive impact on ESG initiatives, a win-win.

Companies often have several questions when it comes to adopting a dual sourcing strategy. For example, when clients consider PCI as a potential secondary supplier,

they often want to know how flexible we can be in terms of absorbing manufacturing and packaging on demand, where we source our materials and components from, and what our relationship is with our vendors – they are looking for the confidence that we can deliver their strategy. As a large global organization, we have significant buying power and influence over our downstream supply chain, which, for smaller biopharma companies, is almost as important as our exemplary delivery, regulatory and safety record!

Through our already established processes and procedures, we also actively make the switch to a dual sourcing approach as smooth as possible; for example, we have the appropriate licensing and accreditations to be a dual sourcing supplier for large and small molecules across all pack formats for a global market. Indeed, our approach to business continuity planning has seen us establish multiple operations across North America, Canada, the UK, Europe, and Asia Pacific, so when you choose to work with PCI, you are not just working with one site – you benefit from over 50 years of expertise, end-to-end capabilities, and scalable capacities available across our global network of 30 facilities.

Clearly, no company is immune to supply chain pain, PCI included, but proactive planning and effective risk management ensure we are prepared. Our approach allows us to have everything necessary to sustain our business and, crucially, to ensure our clients can deliver medicines to patients. As just one example of how we proactively mitigate risk, we have increased stockholding of key materials across all our sites, but most notably in the UK (to counter Brexit-related challenges) and also at our San Diego and Australian facilities for the launch of our automated aseptic fill-finish platforms. We also continue to expand our warehousing capacities to feed our manufacturing and packaging sites so that we can store materials for longer, giving client's surety of supply.

Through acquisition and growth we have invested in our ability to provide an end-to-end solution to support clients from early development and manufacturing phases through to commercial packaging and labeling for oral dosage forms, creams, gels, ointments, and injectables. When a company selects us to be their dual source supplier, they have the confidence that their needs throughout the product lifecycle can be delivered by PCI – whether that be from a single site or via our global network.

At PCI, we are constantly scrutinizing our own operations to make sure we provide our clients with the most efficient service. We apply the principles of continuous improvement to everything that we do and share best practice across our global network – which given we launch over 90 new products a year on behalf of our clients, means a huge amount of expertise to learn from and share with our customers. This approach has meant that across the board, we are not only increasing safety stock levels – in some cases to 12 months of stock or more, but also adding new service lines and technology driven solutions such as late stage customization to deliver value to our client partners and streamline their supply chains – all in the name of risk management.

As new guidelines and advice from regulators emerge, we review them in detail to ensure that we understand every aspect and potential impact so that we can fully support our clients – wherever in the world that they need to distribute their products.

An obligation to ensure supply

Another key advantage of working with PCI is our focus on supply chain planning – one aspect of which is working closely with both our suppliers and customers to understand their forecasts and demand in advance, as well as the challenges they might be facing. We use this information to support them and make data driven decisions to ensure we can deliver on critical supplies. In many instances, we have been able to procure key materials and components when others could not. How? The best planning, the best execution, and a high level of technical acumen. On this latter point, let's consider one of the greatest challenges in the supply chain right now; all the work in the vaccine space has placed tremendous strain on the manufacture of sterile filters, resulting in lead times of 50 weeks or longer in some geographies. Our engineering team found the same membrane in different filter housings – and then designed the interfacing gamma irradiated tubing sets to allow us to use the new filter within the customer's process (after validation, of course). In short, we kept the supply moving. Of course, it is impossible to protect everything and to purchase all the component volumes you may possibly need for every single issue, and so sometimes, you have to be creative, and we are proud to say that time and time again, as in this example, our team has turned a problem on its head and found a solution!

You could view all this risk mitigation as being the obligation to our clients – but we also have an ethical and moral obligation to do our best to provide therapies to patients as the supply chain partner. We never want to see a clinical trial halted or a commercial stock out that affects patients. Some events, such as the pandemic, are out of our control, but we do have a responsibility to effectively manage our supply chains and ensure business continuity as much as we can to ensure that our clients can continue to serve patients.

In My View

Experts from across the world share a single strongly held opinion or key idea.

LV Versus AAV

Demand for gene therapies is rising, so all the more reason to better understand the properties of their delivery devices

By Suparna Saynal, Head of Viral Vectors, Commercial Development, Lonza

Demand for viral-vector-based gene therapies has risen to unprecedented levels, thanks to their potential to help treat previously incurable diseases. The two vectors most in the spotlight? Lentiviral (LV) vectors and adeno-associated viral (AAV) vectors – due to the increased research and positive clinical results they are seeing across a wide range of applications, including cancer, heart disease, and hematologic and genetic disorders. The more drug developers look to expand this range of therapeutic areas, the greater the demand for commercial-scale development. So it's important to understand not only how these two vectors can be applied to drug development, but also the capabilities required for scale-up that allows us to bring these innovative therapies to patients.

LV vectors are derived from the single-stranded RNA retrovirus HIV-1, and have been used extensively because of their ability to infect non-dividing cells, efficiently integrate into the host genome, carry large transgene loads, and allow for long-term transgene expression. They are predominantly used as delivery vehicles for introducing genetic modifications into cell therapies, such as CAR-T, and HSC gene therapies. Importantly, recent regulatory approvals and clinical successes with LV vectors are spurring even more interest among drug developers.

Let's look at the benefits of LV vectors in more detail:

- Volume. LV vectors can carry a high volume of transgenes – up to 8 kilobytes – into the DNA of host cells, which helps address more indications.
- Gene delivery. The viral genome is passed onto daughter cells during division, leading to long-term and stable expression of exogenous genes.
- Applicability. Unlike other types of retroviruses, lentiviruses can infect cells whether or not they are dividing, which allows them to transduce and genetically modify cells that do not replicate.
- Immunogenic profile. The recent lentiviral vector designs have low negative side effects; an advantage they share with AAV vectors.

However, LV vectors also present two major risks to safety.

The first is a risk of accidental exposure because HIV can self-replicate during manufacturing thanks to the lentivirus' high mutation and recombination rate. Though research shows that the risk is low, it remains a major safety concern for lab engineers and workers during development. Before using a lentiviral vector system, a risk assessment must be completed and documented. Typically, lentiviral vectors may be safely handled using either BSL-2 or BSL-2 enhanced controls, depending upon the risk assessment.

The second risk is the potential for oncogenes to occur in cells through insertional mutagenesis. For this reason, lentiviral vectors are predominantly used for cell therapy applications with genetic modification of cells ex-vivo. Only limited use is seen for direct in vivo therapies.

Unlike their LV cousins, AAV vectors are single-stranded DNA parvoviruses that can replicate only in the presence of helper viruses, such as the adenovirus, herpes virus, human papillomavirus, and vaccinia virus. Following several landmark approvals, AAV vectors are currently being used for in vitro, ex vivo, and in vivo research. AAV therapies predominantly target rare genetic disorders for which the patient population tends to be highly limited. As the market is so small, drug developers feel immense pressure to be first to market to commercialize their therapies.

The biological elements of AAV vectors make them a very attractive candidate for gene therapy for several reasons:

- Safety. AAVs do not produce any known human diseases and thus have very low pathogenicity and require less equipment to handle.
- Immune response. AAVs have a low immunogenic profile, complementing their low pathogenicity during gene delivery and reinforcing their biosafety.

- Infectivity. Thanks to their ability to deliver genetic material to dividing and non-dividing cells, AAVs can be applied across different indications – an advantage they share with LV vectors.

As with LV vectors, AAV vectors come with several drawbacks that affect their applications and efficiency.

Firstly, AAV vectors are limited by their restricted capacity for insertion of transgene DNA; because of their relatively small transgene size, they are unable to deliver genes larger than 4.8 kilobytes. Secondly, the generation of neutralizing antibodies against AAV in non-human primates (NHP) and humans may attenuate the curative effects of AAV-mediated gene therapies and limit the size of patient populations suitable for these therapies. Thirdly, there are several different serotypes and capsids for AAVs, all of which have different production and purification requirements and vary greatly with respect to function and efficacy. Fourthly, AAV drug products have varying degrees of empty and partially filled capsids, and these have implications for safety and efficacy. Generally, the highest possible percentage of AAV particles with the full transgene DNA is desired, and this varies significantly depending on the production method, AAV serotype, and the transgene itself. The latter two factors introduce significant manufacturing challenges for AAV therapies.

Overall, the industry's collective ability to successfully scale up LVV and AAV vectors faces two challenges:

i. Manufacturing each viral vector currently requires different processes, so companies cannot apply a one-size-fits-all approach to their upstream and downstream processes. Therefore, manufacturing requires immense scientific and market expertise to make the informed decisions necessary for developing a robust plan.
ii. Given the industry's limited experience with commercial-scale viral vector supply, companies need to work closely with regulatory agencies. This can be especially challenging during the transition from preclinical to commercial, where complexities arise that can cause potential delays resulting in increased costs.

As demand continues to rise, pharma companies must understand how to navigate these challenges to continue delivering their life-saving medications.

Let's Get Closer

Post-COVID-19, the pharma industry has a better opportunity than ever before to get closer to the patient

By Emma Banks, CEO, ramarketing

Pfizer, AstraZeneca, Moderna, Johnson and Johnson, and more – consumers are now as familiar with big pharma names as they are with the likes of Apple, Coca Cola, and Nike, a fact that has completely changed the playing field for pharmaceutical companies when it comes to growth.

Before the COVID-19 pandemic, the general public was never acutely aware of which organizations created their medicines or vaccines. Although people were used to vaccines, they were not used to knowing who makes them, where they are manufactured, or what effort pharma companies put into making them as rapidly and safely as possible to serve a global population.

Because of the unparalleled need to make COVID-19 vaccines and get them into the arms of people as quickly as humanly possible, the media spotlight has been on pharma. As a result, the public is much more aware of the pharma industry and the pharma supply chain is much more aware of its direct impact on the end-user – people. Prior to COVID-19, although all companies involved in the pharma supply chain – from manufacturers to clinical research organizations to packaging to IT partners – understood the purpose of the product they were responsible for delivering, its immediate impact was never seen. COVID-19 generated constant media coverage of vaccines, including how being vaccinated unlocked freedom for many populations and how the injection directly saved lives. The speed at which the entire pharma supply chain worked to enable the delivery of a global vaccination program was phenomenal – and has changed the sector forever.

In my view, this shift to being closer to the patient has been transformational.

Elements of the pharma supply chain that didn't traditionally engage with patients are now doing so and, from a patient point of view, are expected to. Suddenly, people care who manufactures a therapy, where it comes from, how it is stored, and what its side effects are. This provides an immediate and huge opportunity for pharma companies to proactively market themselves. The pharma industry is built around human life – saving it and improving its quality. Now, it can actively humanize, moving away from the stereotypical pharma perception of a sea of blue medicinal packets stacked high in a storage facility toward the development of a more mainstream, accessible image.

The current landscape enables pharma companies to raise their profiles and develop their reputations by being transparent about how they work. The industry is in a position to lay bare its personalities, showing people what's behind the business and what drives medicine makers forward. Delivering COVID-19 vaccines at scale took real passion. For many pharmaceutical firms, the amount of investment and risk taken to get those vaccines to market was astronomical. If something had gone wrong, it could have spelled the end for many businesses – and this is where opportunity lies. It's time for pharmaceutical companies to embrace being closer to the populations they serve, use the greater societal contact they now have, and be open about the industry's challenges, successes, and failures.

Pharma companies should highlight specific activities around – for example – good governance, robust sustainability practices, or strong ethics. This can help connect profits to purpose and drive a stronger public image.

Although we don't generally hear pharmaceutical companies shouting about the incredible work they've done or the vital role they have played in monumental public health milestones, their efforts have not gone unnoticed by investors. The unwavering pursuit of a vaccine (indeed, several) that was safe and effective in a hugely diverse global population is extraordinary – not to mention the speed to market. Consequently, this has generated investor interest and revitalized mergers and acquisitions. Pharma has always been high-risk from an investment perspective given its pioneering and experimental nature, but COVID-19 has more than illustrated the industry's capabilities. Whether this proves to be short-lived only time will tell, but the industry has certainly raised awareness, cemented its credibility, and attracted interest.

Pharmaceutical companies now have the opportunity to make their brand more accessible, and more patient-centered while streamlining efficiencies, costs, and processes to enable the next stage of growth. Overall, the industry is in a position to be truly brave about its brand – and it's time to take on that challenge.

One supplier takes care about the complete line, the entire process. Achieving real innovation requires the complete interaction of every single element. It means creating an environment where people, equipment and technology come together in perfect synergy.

This is IMA Pharma. This is the All-In-One.

ima.it/pharma

IMA SPA

Scoping Out the Future of Single Use – Together

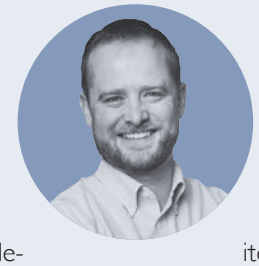
Cytiva's single-use and fluid management technologies were deployed in the production of vaccines and treatments to fight the COVID-19 pandemic. Now, the company is keen to work collaboratively to apply lessons learned – and address increasing demand for flexibility and component interchangeability.

Featuring Erik Storm (Fluid Management Product Leader, Cytiva), Jeff Carter (Strategic Project Leader at Cytiva and BPSA Chair) and Chor Sing Tan (Strategy Manager, Growth Initiatives, Cytiva)

What are the current concerns in single-use bioprocessing?

Erik Storm: Although single-use technology is maturing, supply chains still contain risk due to sole-sourced or sole-manufacturing site components and raw materials. Cytiva and others in the industry have invested to expand supply and component options, but our industry struggles with a slow pace of acceptance of these changes. We're also feeling the effects of a large degree of end-use customization of single-use consumables and the complexity it adds to operations.

Jeff Carter: Overall, the biggest concern is ensuring uninterrupted supply of parts to fulfill customer orders – and hence to maintain drug manufacture. Within this broad field, specific unresolved issues include the definition of standardization and how to achieve standardization of components and final assemblies. However, the large number of component families and the number of items within a component family will eventually force the industry to address the standardization issue. The good news is that effective handling of standardization will have immediate benefit in the security of supply for single-use equipment. The connection here is that securing supply often requires dual sourcing. Dual sourcing requires demonstration of component interchangeability, and that demonstration is dramatically simplified if the industry has figured out the component-standardization question.

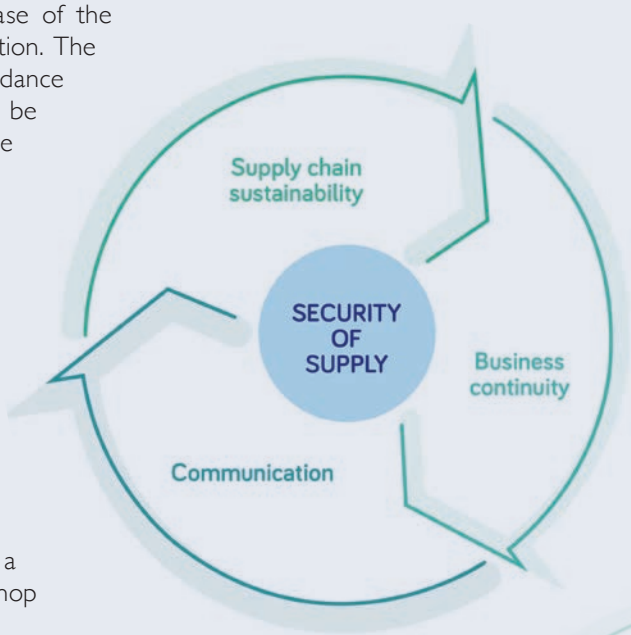


And is that why the FDA released new guidance on post-approval disposable material changes (1)?

JC: Pandemic-related supply chain problems forced the industry to reassess preconceived notions regarding qualification of alternative parts and embrace new strategies, such as dual sourcing. Essentially, suppliers and end users were both asking, "How do I take what is available and continue to operate?"

The FDA appears to have recognized these trends with the release of the high-level guidance you mention. The full implications of the guidance are not yet clear. It would be impossible for the agency to be exhaustive in their handling of the topic, but the guidance provides several examples of changes and how they should be managed. Readers are likely to have varying interpretations and to interpolate or extrapolate to cases not in the guidance. I think this is a very good reason to pull this into an industry organization – BioPhorum seems like a good candidate – and workshop the guidance to better understand its implications and to come to a common interpretation. For example, the guidance mentions some items, such as sterilizing filters and purification resins, but not others, such as bags and other single-use manufacturing equipment. I would be quite interested to see how biomanufacturers will apply the guidance. Because it may affect us as a supplier, we need to understand how biomanufacturers will see validation requirements. This will help us to construct our boundaries related to, for example, single-use component changes, and it will help us to support biomanufacturers to qualify changes.

Chor Sing Tan: Much of the impetus will come from our customers – many of whom were already proactively driving implementation of the European Medicines Agency's ICH Q12 guidance for



Being Better Collaborators

How can suppliers and their customers collaborate more effectively? The answer is easy: talk more and share more.

"It would help us to help manufacturers if we had more information about their plans and the anticipated demand for their products," explains Jeff Carter. "It's a 'help me help you' situation. If customers can give their suppliers, like Cytiva, more information about where they want to go, we will be able to help them when they get there – or help them get there. We don't have enough of these kinds of conversations, which would help the entire supply chain!"

Erik Storm says that the bioprocessing industry has a great deal to learn from other sectors in terms of sharing inventory levels, historical usage rates, and predicted changes. "Single-use technology is the most logistically complex and risky aspect of bioprocessing. Operations can be interrupted by poor standardization and supply chain management," he says.

To mitigate this risk, the industry is attempting to establish dual sourcing of raw materials, which requires close liaison between manufacturers, suppliers, and regulators to determine equivalence and establish best practices for change management. "Cytiva's enterprise business provides integrated applications-based solutions, not just fluid management technology," says Storm. "Customers share their problems and we will collaborate with them to develop a single-use strategy for their unit operations – for example, to implement tangential flow filtration at a given scale."

"I believe that as suppliers, we need to rebuild trust in the industry," says Chor Sing Tan. "Supply chain issues that started during the pandemic are still causing manufacturing delays. In light of these challenges, we have a duty to help rebuild trust in the industry. We've worked alongside customers to support them through the challenges of the pandemic, and we continue to provide comprehensive solutions by analyzing design specifications and the associated equipment and consumables requirements. As a supplier, we can share expertise to mitigate problems that arise in areas like biomanufacturing, fluid management, logistics, and supply. That is important to help rebuild trust."

managing post-approval CMC changes (2). The new FDA guidance and the agency's increased openness to early engagement is a mature approach – one in which the customer participates in regulatory change. It is important to highlight that single-use technology is both raw material and process equipment. Changes made could impact process performance, and process equipment design and operation qualification. The new FDA guidance has provided examples to illustrate the importance of change classification based on risk assessment, established conditions of the process as reference point, process monitoring, raw material supplier qualifications, and process simulation models to predict the impact of change.

How will the guidance impact advanced therapy bioprocessing?

ES: Manufacturers of advanced therapies, such as cell and gene therapies, often rely on single-use technologies, so this new guidance is very important to them. A key consideration will likely be to apply risk-based approaches to material criticality and dual sourcing earlier in process development and clinical development. Bringing structure to evaluating the risk of a material change early in the development process may make change easier to justify later.

Will Cytiva lead or follow discussions around the guidance?

JC: The guidance was really directed at end users rather than organizations like Cytiva, so we won't be leading or following – rather, we will be collaborating. The topic of interchangeability is extremely important for the industry, and Cytiva has joined in discussions about the definition of interchangeability in industry forums. I believe a joint approach between suppliers and our customers is essential if the industry is to challenge paradigms and determine how to best operate within given regulations.

ES: I agree. Customers will drive the dialog around the guidance – but it will be our job to collaborate and provide information to support the discussion, so the topic can be approached from a risk- and science-based perspective. Such an approach will be key to solving the interchangeability challenge.

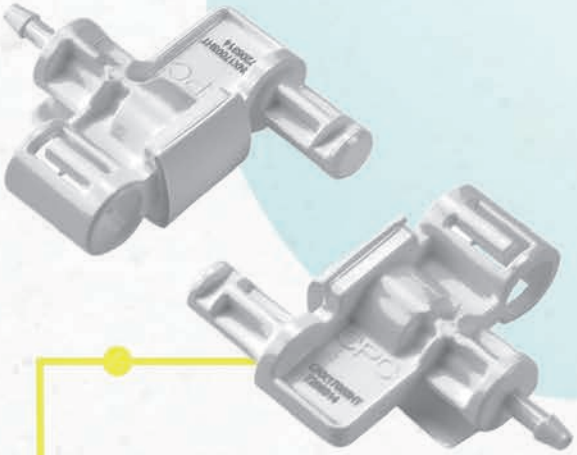
References

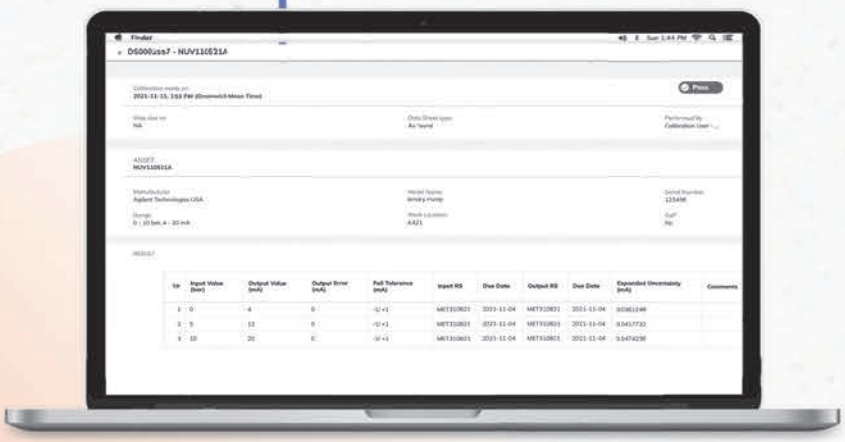
1. *US Department of Health and Human Services, "Changes to Disposable Manufacturing Materials: Questions and Answers Guidance for Industry" (July 2022). Available at https://www.fda.gov/media/160300/download*
2. *EMA Committee for Medicinal Products for Human Use, "ICH Guideline Q12 on Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management" (2020). Available at https://bit.ly/3CLIARs*

CELEBRATING SUCCESS

The Medicine Maker is preparing to celebrate its annual showcase of the top new drug development and manufacturing equipment to hit the market in 2022: the Innovation Awards. Nominations closed recently and you can look forward to the results in our November/December issue.

Before then, we must first turn our eyes back to 2021. The Grand Winner of our 2021 Innovation Awards – as voted by visitors to The Medicine Maker website – was Nuvolo's Calibration product (part of the Connected Workplace software solution). Here, we get the story behind the technology – and also learn more about our two runners up.





MEET OUR GRAND WINNER

What makes this software so special?

Pandemic lockdowns have drastically changed the way we work; in particular, software and IT tools and infrastructure were crucial in helping companies adapt to the new world. Accordingly, readers of The Medicine Maker chose software company Nuvolo and its Calibration product as their top new technology of 2021. The software's arrival in the midst of the pandemic was aptly timed, offering companies a way to piece together their disparate systems, spreadsheets, plans, and employees at a time when global supply chains were disrupted.

We speak with Nuvolo's Ethan Smith (General Manager, Life Sciences) to dig deeper into the addition of Calibration into Nuvolo's asset management product, and to find out what we should expect in the inevitable evolution of software and user interfaces across the life sciences industry.

How did the pandemic shift Nuvolo's focus – if at all?

Since our founding in late 2013, we have focused on integrated workplace management systems. Healthcare is our most mature industry segment, but during the pandemic we also expanded into life sciences, which was always part of our strategic plan long before COVID-19.

But one thing the pandemic really did change for all of us was rethinking real estate, space, and supply chain management. Many life science businesses were essential and did not shut during the lockdowns; however, many of their support functions did. Office workers with no burning reason to be physically present in the office stayed home and found themselves in need of new tools to help manage their space, desks, and equipment. Companies also had to accommodate new guidelines to keep their in-office teams safe. To address these changes, we built new capabilities into our software to help automate social distancing. For example, if someone booked a cube then the software could block out the cubes immediately next to it to ensure social distancing.

So overall, the strategy and direction of the company did not change because of the pandemic, but we did see new priorities emerge.

"In our experience, we've seen that many companies still rely on paper, spreadsheets, and disparate systems to manage all of their assets, facilities, and processes."

What does Connected Workplace do?

Our software solution, Connected Workplace, aims to bring together everything an organization needs to manage its workplace, including the processes required to maintain the facilities and assets. It helps break down silos between departments, optimize operations, and increase visibility to keep any workplace running smoothly. "Workplace" means different things in different industries, and during the pandemic the already divergent definitions of "workplace" fractured even further! All the more reason, then, for our software to step in.

We launched Connected Workplace for Life Sciences in 2021, leveraging several of the solution's general, pan-industry functions, while also bringing in additional capabilities specific to the needs of people working in life sciences.

Our goal is to make a company's employees as productive and happy as possible, and have the workplace meet their needs, rather than vice versa. In our experience, we've seen that many companies still rely on paper, spreadsheets, and disparate systems to manage all of their assets, facilities,

and processes. Manual paperwork doesn't typically lead to a happy workforce in the 21st century.

How does your solution apply to life sciences?

Companies producing therapeutics of any kind for human consumption must meet GMP requirements. We've added a compliance layer to our software to help with the GMP aspect and to ensure that there is an audit history for anything that happens in a regulated space, whether it's processes, maintenance, space, employees entering the facility, or even cyber security. Our software tracks everything, helping companies work compliantly within the regulated environment.

Where does calibration come in? Why is it important?

Calibration is essential to keeping any facility running smoothly, especially in life sciences, where miscalculation can have catastrophic outcomes. Companies need to be confident in their calibration protocols and execution to ensure that their lab and manufacturing equipment is producing the exact quantity of any given medicine or chemical.

Our software can produce documentation that proves the level of calibration – whether it's an HPLC system, an incubator, or any other equipment that requires calibration. The software also tracks calibration history, demonstrating whether the device has been calibrated correctly in the past, how the device has performed over time, and so on. Historical calibration data is also useful for helping set and measure against standards.

There is also a time-saving aspect; the Calibration product automatically calculates the pass or fail status of each calibration test, saving the technicians from taking on that work themselves. This type of platform and control can also encourage best practices for calibration by ensuring everything is done the same way. When people are doing things differently, it introduces the potential for errors.

Are there any other benefits to using your software?

Calibration needs to be an integral part of comprehensive asset management. Historically, calibration documentation has been provided by external service vendors without any actual data. Connected Workplace for Life Sciences provides much more than just a certificate indicating that a device is calibrated properly. There is a wealth of calibration data that can be integrated with other maintenance data, which

enables companies to make data-driven decisions based on asset health, historical trends, and service and replacements costs. Are assets being calibrated too often? Or not often enough? These questions can be difficult to answer with traditional paper-based systems but easier to analyze when there is a large, easily accessible dataset.

We should also talk about the reference standards that metrologists and technicians use for the calibrations. These are expensive to buy and also expensive to maintain. Some enterprises may have a few hundred reference standards, so it is important to know which are being used. This is nearly impossible with a paper-based system. With the Calibration product, it is easy to track reference standard utilization and reverse traceability; if some aren't being used at all, a company can retire them and cut costs.

Other important aspects of the software are the user experience and user interface. These are crucial to ensure people can engage with the software, get the most out of it, and avoid data errors. In our Calibration product, we've added a customized user interface to keep its operation as straightforward as possible, which in turn should reduce the number of errors in the data.

Was it challenging to adapt the software for life sciences and pharma companies?

The pharma market is certainly challenging for two main reasons. First, there are stringent regulatory requirements that demand good documentation. Software platforms like ours can really help with the documentation aspect. The second challenge – which is considerably more difficult – concerns the balance of producing confidence-inspiring calibration reports while keeping the software simple and user-friendly. We accomplished that by making the user interface simple to use and very difficult for end users to get things wrong when using the software.

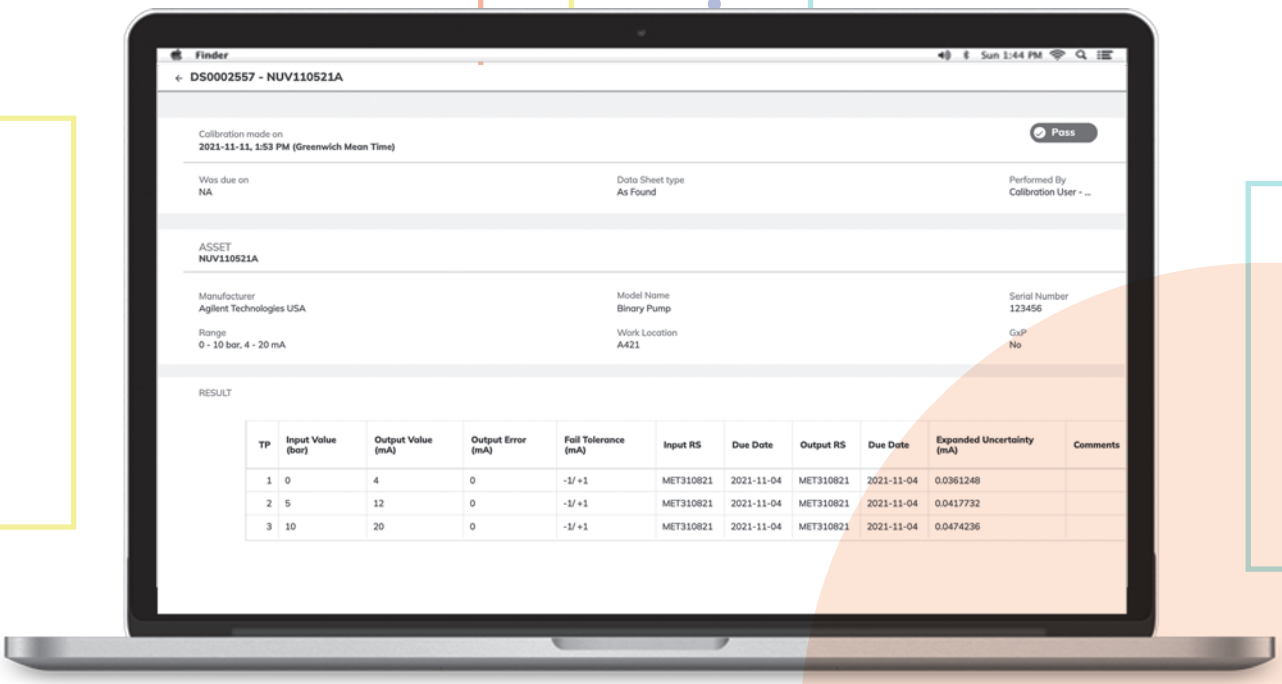
What sets a good interface apart?

The simple answer would be research and testing with end users, but there's a lot more that goes into it. The product manager brings an idea to the table, which then gets ripped apart by our user experience team. It's their job to consider every angle and find justification for every part of an idea, then work through the practicalities until we produce a design draft.

This draft won't be fully functional, but it will be sufficiently fleshed out to present to a test user. We then introduce this test user to the ins and outs of the program, such as workflows and data entry. Next, we bring the interface to even more test users, whose participation will help progress it through iterative research sessions. This process helps us optimize the software before committing to any further development.

When you pitch your product to pharma and life science companies, what questions do they ask?

First and foremost, they want to know about Nuvolo as a company. Then, they want to know about the platform. Most of the questions concern security, especially in cloud and software as a service. In the last decade or more, we



have witnessed a real sea change regarding the cloud. I remember the days where you would literally get the door slammed in your face if you talked about the cloud. Today, most organizations have matured and know how to conduct a proper assessment of validated cloud infrastructure.

Once a company is comfortable with our qualified infrastructure, they focus on how we meet industry requirements. The conversation shifts very quickly into highly specific feature functionality. "Can you do X?" "Can you do Y?"

Next, we'll typically face some "how" questions, and then comes a comparative process where we measure ourselves either against their current tools or others on the market. Sealing the deal can be real work, but that is perfectly fair! Success hinges on the users, so that is who we need to cater to.

"It is easy to track reference standard utilization and reverse traceability; if some aren't being used at all, a company can retire them and cut costs."

What are the big trends in life sciences software right now?

AI and machine learning are the main areas where I expect to see big changes in the future. As the data sets that companies work with inflate, there will be a need for AI tools that can sort through the data to speedily generate increasingly powerful insights. We may also see more comprehensive use of the "internet of things" within the industry too, where we are able to integrate software even further into more devices.

End user configurability is another major undercurrent within the industry. It's what makes Excel probably the most widely used software application out there. You can do almost anything with it. The way that you would build a spreadsheet to analyze a dataset is different from the way I would do it. Everybody uses Excel differently, and there's nothing wrong with that. One hurdle that user interfaces have historically faced is the idea that everybody must do everything exactly the same way every time. In the real world, that's not how people work (or want to work), and it's not how business functions. At the end of the day, there are always exceptions. The natural intelligence of employees is incredibly valuable, especially in highly regulated industries.

Improving end user configurability does not entail changing the fundamental software itself. It's simply about giving users more flexibility to do their work in the way that makes sense for them, or the way that certain exceptions or other processes demand. We all hear people talk about workarounds when it comes to software. As software designers, we want to help users change the function of the software as it suits them, negating the need for workarounds entirely. I know I'm not alone here and I think this will be an important trend going forward as software becomes more important in the life sciences industry.

Is the life sciences software market crowded?

In short, yes. One might think that this is a good thing for clients: more options, better choices, and a buyer's market. But the reality is that, over the last five years, software companies have become very aware of the fact that pharmaceutical and biotech companies are ripe targets flush with cash. Software companies rush to produce gizmos and widgets without any deep understanding to back the products up, resulting in bad products not suited for purpose, and many life sciences clients getting burned. If you want the best software, you need to look at the people who design it, develop it, and build it. You need to know that the software developers behind the system understand the compliance requirements in the pharmaceutical space. With cloud products, you also need to look at the robustness of data centers, infrastructure, and disaster recovery. Ultimately, you need the people that know life sciences to be the ones designing, building, and testing that software so that it really is fit for purpose.

Runner Up

IT'S ALL ABOUT CONNECTING

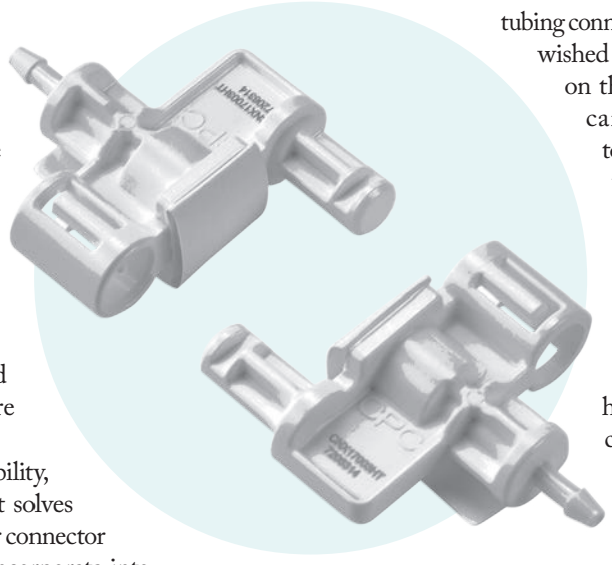
How demand for simpler, smarter connectors inspired a new product launch

Sometimes, there's nothing better in the world than two parts that simply and painlessly click together. If you find yourself nodding, you'll agree that CPC's MicroCNX Series Connectors are worthy runners-up in our 2021 Innovation Awards.

So what exactly are these "connectors?" In short, they are the sterile links that connect tubing in the biomanufacturing process. To learn a little more about these gizmos, we spoke to CPC's Senior Product Manager, Troy Ostreng – the man who walked the connectors through each stage of product development.

Why are good connectors key for the biopharma industry?

Connectors are vital because they close systems and maintain sterility. CPC's MicroCNX connectors and AseptiQuik connectors are great examples of this. Other products, like our MPC couplings, offer what we consider to be "a near-closed system," but sterile connectors are able to go all the way.



Good connectors should offer reliability, sterility, and a product design that solves users' pain points. We make sure our connector product design is easy to use and incorporate into the user's closed system. The MicroCNX connector comes together in a simple, three-step "pinch-click-pull" installation: the user pinches to remove the connector's protective cover, clicks its two halves together, and then pulls out the protective membranes to allow flow to move through the connector. The simplicity of this process helps reduce the risk of operator error, which has a positive knock-on effect in terms of performance and reliability concerns.

What makes the Micro CNX connectors stand out?

The MicroCNX sterile connector is the smallest sterile connector on the market, with a genderless design and hose barb size options of 1/16", 1/8", and 3/32". They are aseptic micro-connectors that connect tubing for small format assemblies. MicroCNX connectors provide a modern alternative to the often cumbersome and unreliable method of tube welding. These connectors fit in most systems because we took their size and weight into careful consideration in the design phase.

What inspired the launch of these connectors?

Customers were telling us about the pain points they faced in their traditional methods for small flow applications and tubing connection – and all the improvements they wished for. We listened and then embarked on the most extensive voice of customer campaign we had ever committed to. We wanted to really understand what these customers did and didn't need from their connectors, and the fruit of that campaign was our MicroCNX connectors.

We talked to over 50 industry representatives across biopharma, cell therapy, and gene therapy to help paint a better picture of how customers were using connectors, what they liked, and, more importantly, what they didn't like. Some of the key things identified in this information gathering process were that customers were looking to simplify production, decrease contamination risks, increase the repeatability and reproducibility of the connection process, eliminate the need for additional equipment and reduce their total weld and/or connection time.

What challenges do you face in presenting an alternative to tube welding?

Tube welding, especially in smaller format tubing, is deeply ingrained in our customers' existing processes. It's an approach that has been used to enable closed processing for decades, but it comes with potential drawbacks and risks that can compromise sterility. A large part of our task is to teach people that an alternative exists. Connectors like ours offer a more reliable, consistent means of connection, and we want

customers to know that. Connectors are still a relatively new technology, especially in the field of cell and gene therapy, so we know that it's important to keep sharing our knowledge with customers and demonstrating how effective connectors can be in small-volume closed aseptic processes.

Aseptic connections with the new MicroCNX connectors can be completed in three steps and up to four times faster than an operator using tube welding, which can require a dozen steps or more to achieve a successful weld – so we have a strong case!

What trends are driving innovations in the single-use space?

Most CDMOs and biopharma companies incorporate single-use bioprocessing equipment into their processes wherever possible. This is a trend I expect to continue. Typically, it takes five to seven years to progress from ground-breaking to running a qualified stainless steel facility. In contrast, a single-use, system-based facility might require only two to three years.

After the facility becomes operational, single use allows the biomanufacturer to process multiple drugs simultaneously in one space, or to make rapid equipment changeovers between production runs without compromising sterility. That push for efficiency and modularity within and across sites is a major driver.

We're also seeing a strong interest in standardizing single-use technologies, which begins with components purchased from single-use equipment suppliers. The same equipment, standard operating procedures (SOPs), and a shared supply chain create significant efficiency.

A growing number of companies are now engaged in small-volume (< 10 L) aseptic processes, such as early-stage drug development. You'll also see very small volumes in cell therapy, for example, where cell availability is limited or media is expensive, and in the development of small-batch autologous therapies. The single-use component industry is catching up to create solutions specifically for small-bore tubing in small-volume work. This includes applications, such as sampling, seed train expansion, analytical processing, buffer/media transfers, and early cell-culture processes, involving shaker flasks and rocker tables.

How do you hope to see biopharma operations improve in the future?

We've been working hard to address the concerns raised in our voice of customer conversations. There are long-standing industry needs and demands around faster, more efficient, and less operator-dependent production. Our product developments reflect those conversations. And that's where we see our MicroCNX connectors playing a major role today and in the future. These connectors help solve the issue of the industry's reliance on old-fashioned tube welding to make sterile connections.

Investment across all single-use manufacturers was already quite significant even before COVID-19, but the pandemic only served to reemphasize the fact that single use is the backbone technology that helps exciting new therapies reach the market much faster. COVID-19 taught all of us how to adapt quickly, collaborate effectively online, and pivot when necessary.

Runner Up

THE CUTTING EDGE OF BIOPHARMA ANALYTICS

How can new analytical tech help biopharma manufacturers?

Ying Qing Yu is Director of Biopharmaceutical Sciences in the Scientific Operations Department at Waters Corporation, whose BioAccord System with ACQUITY Premier device won a runner up spot in The Medicine Maker 2021 Innovation Awards.

The system is designed to solve the prime problems of cost and complexity faced by all biopharma companies taking a crack at liquid chromatography-mass spectrometry (LC-MS) adoption. Here, Yu runs us through both the workings of the technology and its place in the wider context of mass spectrometry for biopharmaceutical companies.

What makes your work exciting?

I lead a group of scientists that develop new and innovative LC-MS analytical solutions to improve the safety and efficacy of biotherapeutics. The work we do is exciting because the biopharma industry we support is always evolving and always growing. Biotherapeutics have a huge positive impact on people's lives, and I know that improving the health and wellbeing of mankind is the best way for me to apply my expertise and knowledge.

In a nutshell, what does the Waters system do?

The BioAccord LC-MS – which is controlled by our compliance-ready software, waters_connect – is an integrated, benchtop LC-MS system. It consists of an ACQUITY Premier UPLC system and an ACQUITY RDA time-of-flight mass detector. The system includes optical detectors for tunable UV and fluorescence that are in-line with the mass detector, and embedded SmartMS technology, which automates setup and self-diagnosis, lowering the usability barrier for non-expert MS users.

It's suitable for late-stage drug development, process control, and quality control (QC) settings in both regulated and non-regulated environments for intact protein, released glycan, and peptide monitoring applications.

How were you involved in the development of the system?

For the development of BioAccord LC-MS System, I led a team of biopharma application scientists from the very

early stages of the project. Along with the rest of the team, we were very involved in all the major milestones of the project: the drafting of the user request documentation, the alpha and beta system testings (to which we invited external biopharma thought leaders), commercialization, pre- and post-launch application development, marketing, and customer support.

What's the origin story of the system?

A few years ago, when Waters was developing its next generation LC-MS systems, we examined the needs of the biopharmaceutical industry. From FDA reports, we learned that almost every BLA filing contains mass spectrometry data. The key product attributes measured with MS have increased every year over the past two decades. Though we found examples of LC-MS for QC use, LC-UV was predominantly used for product release testing. We wanted to understand the reasons why QC labs were reluctant to use mass spectrometry for release testing, so we conducted hundreds of interviews with industry scientists.

We found that the top six criteria for LC-MS system deployment in the QC labs are: robustness, assay-to-assay reproducibility, ease of use, small footprints, integration, and compliance-ready informatics with a streamlined workflow.

Equipped with this information, we assembled a cross-functional team (of which I was a part of) to develop the BioAccord system, which we successfully launched in 2019. At the same time, we were working on the development of a new chromatography surface technology for the ACQUITY UPLC that minimizes non-specific interactions between the metal surfaces of the LC and a variety of molecules, such as oligonucleotides, phospholipids, acidic peptides, and glycans. This latest LC surface enhancement goes under the trade name MaxPeak High Performance Surface (HPS) technology, and it was commercialized in 2021 with the introduction of the ACQUITY Premier LC for the BioAccord System.

The BioAccord system features what we call SmartMS technology. The system has a color-coded front panel display showing the system status. When the status is green, it indicates that the system is either ready to go, or running an analysis. When it is orange, it signals that the system may need

to be checked for minor issues. If it is red, it indicates that it may be time for a service call.

The system's software automatically checks the performance of the BioAccord system between injections by checking system performance with reference standards, including the MS peak resolution, the absolute and relative MS response, and the mass accuracy. This automatic system monitoring process is designed to make sure that the system performs to specification, and to ensure that it adjusts system settings accordingly.

What specific challenges can the system solve?

The system is easy to use and maintain, and is designed for non-expert MS users. It is a compliance ready, high-performance system that can be deployed in both regulated and non-regulated environments for the routine analysis of a variety of biotherapeutics (protein, peptide, glycan, oligonucleotides and cell culture media).

In 2021, Waters Corporation and Sartorius entered into an agreement to work together and bring LC-MS into the upstream bioprocessing laboratory, where there is a real need for both an at-line product and process quality attribute analysis. Today, it can take 2–4 weeks for bioprocess engineers to receive results from a core analytical laboratory on samples taken from a bioreactor (e.g., a full plate with 48 samples). This slows down the clone selection process considerably. The BioAccord System, however, can generate the same information in a matter of hours.

This is an ideal application for the system, where those responsible for bioprocess development needn't be mass spectrometry experts, and where the information provided by LC-MS can make a difference in deciding the best cell line and clone for expressing a biotherapeutic, for monitoring product attributes of the drug, and for monitoring cell culture media.

What are the main challenges faced when developing analytical systems?

Correctly understanding user requirements and defining the right product requirements are some of the biggest challenges. Engineering teams can come up with innovations, but understanding what a fit-for-purpose system looks like and which improvements customers value most is critical. Developing complex analytical systems involves several large teams, and this in itself is another challenge. Nobody ever said that getting large teams of electrical, mechanical, software, quality, test, and system engineers plus chemists, service teams and applications support teams to work toward a common goal was easy!

Why is it important for companies to keep apace with changes in technology?

It is understandable that many companies want to stick with older systems, despite advancements made in analytical technology. Their most likely reason for this is the disincentive of upfront capital equipment costs. Another consideration is the time and effort demanded by the validation of new methods.

However, there are good reasons for laboratories to pursue upgrades. If new technologies can improve analytical

throughput effectively, or measure multiple critical quality attributes of a drug product from a single LC-MS assay, or measure the product attributes of new modality therapeutics during development, then the long-term benefits of upgrading to the newest, state-of-the art analytical technologies will easily outweigh the initial burden of installation and training.

"We wanted to understand the reasons why QC labs were reluctant to use mass spectrometry for release testing."

How will analytical technology continue to evolve?

Over the next decade we'll see two main areas of improvement. One is on advancing high resolution mass spectrometry technology, enabling the mass measurement of very large and complex molecules accurately. For example, charge detection mass spectrometry (CDMS) for the analysis of very large molecules holds a great deal of exciting potential. The second area is to continue to improve ease of use for LC-MS instruments for the routine measurement of different modalities. Lowering the skill barrier for LC-MS operation and data processing would help to improve laboratory productivity. I would like to see improvements in integrated informatics systems that are optimized for automatic workflow-driven data acquisition, processing, reporting, and sharing. Advances here would facilitate faster and more accurate decision-making and lower the development costs of biotherapeutics.

WEBINAR

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WEBINAR LEARNING OBJECTIVES:

- Learn about the advantages of single-use systems (SUS) for ultra-pure fluid handling and processing
- Learn about the respective advantages and recommended applications of silicone and thermoplastic elastomer tubing
- Understand the benefits of Pharma Overmolded Assemblies in reducing contamination risk, offering flexible manufacturing processes, minimizing cleaning validation and decreasing labor costs.

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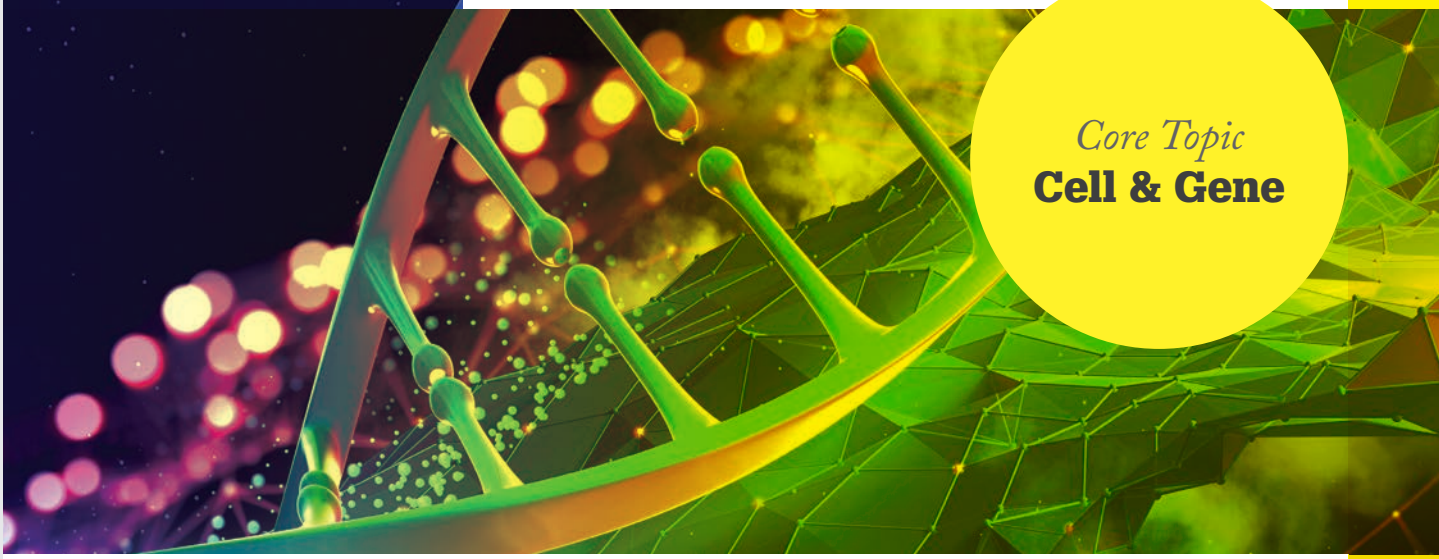

Core Topic
Cell & Gene

Twobirds Bio. Following earlier hiccups in Europe, bluebird bio seems to have well and truly bounced back. In June, its Zynteglo (beti-cel) gene therapy won FDA approval despite rejection in the EU, and bluebird has now followed that up with another FDA approval; this time for Skysona. However, bluebird's mega-pricing bugbear remains, with the former priced at $2.8 million and the latter reaching $3 million. Some commentators are calling the prices a yellow bird: the canary in the coalmine. Whatever the case, there is also celebration of the news from Lonza, whose Houston facility manufactured both of the therapies.

Educating Australia. Prominent advances in gene therapy treatments for inherited retinal diseases (IRD) have pushed researchers from the Center for Eye Research, Australia, to better understand the level of relevant education among potential patients. A survey designed by the Center to measure the knowledge, attitudes, and outcomes of gene therapy was completed by 5.3 percent of the Australian IRD population, and its results have confirmed certain gaps in patients' comprehension. The findings underline the need to continue educational initiatives to build confidence among patients – and clinicians – when it comes to gene therapy-based treatment avenues.

Cell therapy reform in Japan. Kyoto University iPS cell expert Misao Fujita has called for revisions to Japan's cell therapy regulations. Fujita and colleagues carried out a study on cell therapies available in Japan, and found many sketchy enough to risk serious international criticism. The study noted that the existing regulations did not require treatments to be scientifically verified, did not make proper distinction between research and treatments, and did not clearly define what constitutes a "medical innovation" and an "unproven treatment." Fujita and company are arguing that Japan's 2014 Act on the Safety of Regenerative Medicine must be revised if it is to inspire confidence in the therapies it regulates.

Harbor-seeker Hits GitHub. In genome engineering, the identification of "safe harbors" in the genome – points able to continue transgene expression without disrupting the host cells' function – is growing ever more important. Good news, then, from St Jude Children's Research Hospital, where scientists published a software tool able to serve as the "Google Maps" of genome harbors. The tool, which can be downloaded from open-source site GitHub, uses data from the 1000 Genomes Project to assess the 3D structure of human DNA. The scientists behind it claim that the sites identified by the tool work better than "classic" safe harbor sites.

IN OTHER NEWS

Belgium's Bone Therapeutics reclaims worldwide rights to ALLOB cell therapy, following unilateral termination of previous Asian region deal with Chinese partners

Duke University researchers demonstrate RNA-based editing tool able to tag, edit, and expunge specific cells of any type; scientists hope it can improve knowledge of the brain

FDA grants Orphan Drug Designation to Verutica Therapeutics' SynKIR-110 – a KIR-CAR T-cell therapy – for mesothelin-expressing mesothelioma

New outline, published in Membranes, posits nonwoven membranes as tool to purify AAVs for gene therapy; affords high capsid recovery, excellent DNA clearance, among other benefits

Champions of Cell and Gene Therapy

We asked experts: what improvements do we need to see in cell and gene therapy supply chains?

In this series, we give cell and gene therapy champions the opportunity to answer a question on a hot topic. If you crave more knowledge and updates from the fast-paced world of cell and gene therapy, then be sure to sign up to our Cell and Gene Newsletter on our website.


Miguel Forte


Joy Aho

Miguel Forte of Bone Therapeutics says:
"Tech and talent – you can't have just one."

The supply chain is the route by which well characterized and functional cell and gene therapy products reach patients. It plays host to products ranging from very challenging (and now mostly outdated) single-patient, autologous therapies to large-scale cryopreserved allogeneic products for multiple patients. In all cases, three aspects remain critical for a successful supply chain – technology, process control, and readiness to manage the unforeseen.

We continue to see great developments in the technologies that enable the supply chain, but improvements are still needed. These include wider and less stringent cryopreservation requirements with the possibility of reduced necessity for lower temperatures and increased flexibility with local and point-of-care storage options.

Tight control and management of the supply chain process is vital for the quality of the product, and a general readiness to manage exceptional and urgent unforeseen circumstances remains critical. Well adapted processes and suitable operator talent are still necessary assets for a successful supply chain. It should work smoothly and mechanically but enable quick reactions to inevitable surprises.

In the near-future, more patient bedside manufacturing technologies will be considered and developed and "micro supply chain" options will be needed. This area will certainly see growth.

Overall, it is always about the interface between the technology and talent and experience of the operators. We will need to develop both.

Joy Aho of Be the Match BioTherapies says:
"It starts at the start."

With the continual growth in the development of allogeneic cell and gene therapies, the sourcing of allogeneic cellular starting material is becoming an increasingly critical component of the cell and gene therapy supply chain. As these therapies continue to move into later clinical phases and approach commercial approval, there are many important considerations to ensure scalability and consistency in supply.

The industry needs a better understanding of optimal donor characteristics for these emerging cell and gene therapies. Many groups rely on a small number of "super donors" – smaller sets of donors whose donated material has been used successfully in manufacturing – to support their starting material needs. This is unlikely to provide a long-term solution for later clinical phases and into commercial approval, especially for the large indications being targeted by many of these therapies. For the sake of future scalability, it will be important to better understand and more easily test for these characteristics upfront.

Greater clarity and consistency in starting material testing needs would also greatly benefit current supply chains. For developers planning to distribute their therapies globally, differing regulatory requirements across the globe have led to complex testing needs for cellular starting material. In general, as seen with autologous therapies, finding areas to standardize around starting material collection without impacting critical quality attributes for a particular therapy will be essential to ensure scalability for manufacturing allogeneic therapies and access to the patients in need.

Bill Vincent of Genezen says:
"Brace for impact."

When predicting challenges that the cell and gene therapy industry would face in 2022, it was no surprise that many drug developers consistently


Bill Vincent


Jessica Madigan

identified supply chain issues as a big area of concern. In the years leading up to 2020, the global viral vector manufacturing capacity had expanded in response to increased demand for these advancing technologies. The onset of the COVID-19 pandemic then magnified the supply burden that manifested.

Increased demand for vaccine manufacturing supplies was seen worldwide, in parallel with supply transport and delivery disruptions. Additional issues stemmed from the reduced availability of raw materials, like fetal bovine serum (FBS), used in the upstream processing of many biologics.

With some items subject to a one-year lead time, developers and manufacturers came under further pressure to increase stockpiles or find alternative suppliers to prevent disruption. This challenge persists to date and is particularly prominent for projects at clinical phases, where speed is of the utmost importance for success.

Although those in the cell and gene industry are hopeful that supply issues will be resolved with the world coming out of COVID "lockdown," the impact of future global events will never be easy to predict – from natural disasters to new pandemics or conflicts. However, we can foresee that continued high demand for COVID-19 vaccines and growth in the cell and gene market will only add to future supply challenges.

To overcome these issues, a growing burden will be on suppliers to invest in manufacturing capacity and offset this bottleneck. By making all the necessary technical, quality, and safety information easily accessible, as well as being proactive in identifying potential solutions, suppliers could further ease the difficulties biopharma manufacturers face. If major suppliers do not adapt quickly, we can expect alternative competitor vendors to fill the void.

Jessica Madigan of BioVectra says:
"Prioritize plasmids."

Perhaps the biggest supply issue for cell and gene therapies is a lack of reliable sources of GMP-grade plasmid DNA. The supply of pDNA – and, therefore, mRNA – is constrained by both manufacturing issues and short supply of consumables and starting materials. These constraints result in at least year-long lead times for pDNA made under GMP conditions.

The industry should adopt established manufacturing platforms that have been through the drug approval process for cGMP plasmid production. For example, plasmid manufacturing has not been designed and scaled to create a reproducible, reliable process for both alkaline lysis and purification. We need a large-scale manufacturing process that can lyse cells as quickly as possible to avoid the buildup of impurities. An optimized lyzing process would lead to higher yields by eliminating the need for additional purification steps with a goal of delivering shorter timelines and reduced manufacturing costs. Since the technology for plasmids and vectors is continuously changing, cGMP manufacturing will need to be flexible and supported by a supply chain and production capacity that can keep pace.

We need to see additional suppliers in the overall supply chain for critical starting materials and consumables to meet the demand of the many manufacturers who have invested in single use fermenters, only to be challenged by months-long lead times for filters, bioreactor bags, and diafiltration cassettes. Another good example of necessary improvements are the anion exchange resins used during plasmid purification to remove host cell DNA, RNA, and proteins. Currently, the best options for high specificity at large scale are low-capacity chromatography resins, requiring large columns and slow cycling times. The industry needs to develop higher capacity ion exchange resins to make purification more reproducible and decrease lead times.

These advances should help relieve the strain on supply that currently bottlenecks the cell and gene therapy market.

If you enjoyed these takes, consider browsing the Cell and Gene Champions back catalog:

Champions Part 1: The Skills Gap
tmm.txp.to/cg-1

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Core Topic
Bioprocessing

Alzheimer's success at last? Is it finally time for Alzheimer's drug development to shine? Last year saw the FDA approve Biogen and Eisai's anti-amyloid antibody Aduhelm, but many stakeholders questioned the drug's true efficacy. An investigation was even launched to look at how the drug was approved. Now, another anti-amyloid antibody is in the spotlight – and the news seems much more promising. Eisai and Biogen recently released data from a phase III trial of lecanemab. The mAb appears to slow cognitive decline by 27 percent. The primary endpoint of the trial was met, as well as all key secondary endpoints.

Interchangeable biosimilars in the EU. The EMA and the Heads of Medicines Agencies have released a joint statement confirming that biosimilars approved in the EU are considered interchangeable with their reference medicine or with equivalent biosimilars. Many EU member states already practice the interchangeable use of biosimilars, but the statement formally harmonizes the approach. A statement explaining the decision adds, "The EU medicines regulatory network has identified the need to explicitly state that, from a scientific point of view, biosimilars approved in the EU can be considered interchangeable. This is because the absence of a clear EU-wide position on interchangeability has been identified as a factor causing uncertainty among stakeholders on the use of biosimilars in clinical practice."

Stay cool. Winter is drawing in for those of us in the northern hemisphere, and some of us will soon be facing below-zero (celcius) temperatures outdoors. But the biologic materials at Almac Clinical Services will soon be facing something significantly chillier: -150 °C to -196 °C. Why? Because the North Carolina company has opened a new cryogenic facility within its Durham campus. Almac's vice president commented that the company intends to use the new setup for work on the manufacture of cell and gene therapies for a range of conditions, including autoimmune diseases and cancer.

Advancing biosimilars in the US. The FDA has awarded the Biologics & Biosimilars Collective Intelligence Consortium a $1.3 million grant that will span two years to help advance biosimilars research. Specifically, the contribution will support a new study focusing on increasing the efficiency of biosimilar drug development using real-world evidence. "The challenges in using real-world data and the relevance of real-world evidence for regulatory decision-making about biosimilars is a major obstacle in the industry," Cate Lockhart, Executive Director of the BBCIC said in a statement. "I'm thrilled the FDA has selected our study for funding, as it will have important benefits for the research community at-large, providing analytical tools for tests of interchangeability and other regulatory questions."

IN OTHER NEWS

Cytiva has acquired cell line development and viral vector manufacturing tech company CEVEC Pharmaceuticals

NIBRT has started construction of a €21-million advanced therapeutics facility at its Dublin, Ireland site, funded by the Irish Government through IDA Ireland

Sanofi US agrees co-promotion service with Provention Bio for commercialization of teplizumab in the US; FDA approval anticipated in November 2022

Novavax to pay Fujifilm Diosynth Biotechnologies up to $185 million to terminate manufacturing contract

Phase I data of two Regeneron bispecific antibodies show positive results in solid tumors for ovarian cancer and MET-altered advanced non-small cell lung cancer

Getting to Grips with the E&L Threshold

The PQRI has released new recommendations on extractables and leachables in parenteral drug products

Extractables and leachables (E&L) have been a headache for drug manufacturers for years. Identification and analysis of E&L is complicated – and the challenges aren't getting any smaller with an increasing diversity of drug modalities. Back in 2006, the Product Quality Research Institute (PQRI) issued recommendations on safety thresholds and best practices for E&Ls in orally inhaled and nasal drug products. Now, they have released new recommendations: "Safety Thresholds and Best Demonstrated Practices for Extractables and Leachables in Parenteral Drug Products (Intravenous, Subcutaneous, and Intramuscular)."

Given the complexity of the topic, the document has been years in the making. Here, we find out more from Diane Paskiet, Director of Scientific Affairs at West Pharmaceutical Services, who has been involved with PQRI for nearly 20 years.

How much work went into pulling these recommendations together? And how long did it take?

Developing a comprehensive recommendation document like this takes a long time. In this case, we needed nearly 10 years to gather data, you need a lot of input – and, ultimately, consensus on the final document. It's also worth remembering that PQRI relies on volunteers from industry, academia, and regulators. To develop the document, we had to draw on volunteers with extensive backgrounds in toxicology and analytical chemistry. We had to develop a proposal and work plan, and get materials donated from different suppliers. We compiled a database of over 600 extractable and leachable chemicals as part of the safety assessment to support the threshold, and we had multiple sub teams that generated data on the donated materials, as well as toxicologists who developed the safety thresholds.

Gathering all this evidence and data has been a long journey! Well over a hundred people have been involved with this – which is a lot of people when you need consensus!

How have conversations around primary packaging changed in the last five years?

In general, the materials used in pharmaceutical packaging have remained the same for decades, except for aluminium silicate glass, which is a more recent development that improves strength and reduces the risk of delamination. However, drug modalities are changing significantly, and we need to know if traditional packaging materials are suitable. In particular, biopharmaceuticals can be very sensitive, and issues with E&Ls can affect product quality; for example, through degradation, modification, or aggregation. The increase in biologic product diversity and complex dosage forms introduces new risks for safety and compatibility, as well as challenges in packaging performance and protection of the contents.

In short, we need to consider the fact that traditional packaging solutions were never designed with antibody drug conjugates, RNA therapies, and other emerging modalities in mind.

Why is it so important to get packaging right?

Treatments and cures would not be possible without the right packaging – or without the right safety and compatibility studies. In some cases, you also need a device to administer the drug to the patient. There have been many conversations on the topic focusing on the scientific and regulatory issues surrounding drug-device combinations. The regulation here is evolving all the time. Add to that the fact that there are increasingly complex products coming down company pipelines and you can see there's still a lot of work to be done in understanding E&L risk.

The science of packaging is always evolving too. I've been working in this sector for over 30 years. At the time, you always think you know what you need to know but then everything changes; we are continually learning about how drug or biological products may need to be stored, protected, and delivered. The potential for chemical migration, leachable reactivity, or surface interaction may not be easily discerned and can affect product quality. The

most important thing is to ensure that packaging remains both suitable and safe.

What's included in the new recommendations?

The document includes a framework for the toxicological evaluation of leachables for parenterals, and best practices for the analytical evaluations of E&Ls. Something that we have peppered throughout the document – because it's so important (and something that the regulators are keen on) – is that drug developers need to engage with regulators early on. There is increasing complexity in both parenteral products and closure systems – and justification and proper documentation are expected, including information on thresholds, extraction conditions, solvents, and so on. The E&L analysis should be discussed early with regulators so that drug developers can be sure that the regulators will have the information they will eventually need to review the final drug dossier for approval. You don't want to get to the end of your drug development program and then find out that there were risks in your packaging and analysis strategy that you overlooked or didn't approach in the right way.

One of the significant recommendations we make in the paper pertains to the concept of thresholds. There are three thresholds: the safety concern threshold, the qualification threshold, and the analytical evaluation threshold. The former two are safety related and the latter is for compound identification.

The safety concern threshold (SCT) is 1.5 µg/day and is used to derive the analytical evaluation threshold. The SCT value was justified from the evaluating of over 600 potential leachables using existing toxicological qualification approaches. Below this threshold, the dose is so low that the safety concerns should be negligible, but that does not guarantee it is safe! The threshold is just for identification and reporting for assessment. Above this threshold, you need to identify and assess your leachable for toxicological concerns. There are certain compounds that are known to be a high risk, which may be below the analytical evaluation threshold and may need to be specifically sought depending on the material chemistry.

The qualification threshold is recommended at 5 µg/day, providing there is no genotoxic or carcinogenic potential, but it is important to consider the potential for sensitization and irritation.

The paper provides best practices for extraction studies and assessments, covering materials for constructing finished components, and complete packaging systems. In the document and supporting publications, we show how to generate the extractable profiles and provide key considerations, such as the sample of solvent ratio, conditions of exposure, and technologies for analysis and their sensitivity. Once you have your extractables profile, you can evaluate and build out your leachables studies.

Overall, it's a difficult topic to summarize – the science is complex (and the paper is almost 100 pages)! I encourage people to read the recommendations for the full details in the hope that it helps applicants with their E&L studies.

Where else is there room for improvement?

There is always going to be a need for new best practices in this field. Science evolves, regulations change, and new modalities emerge. One area we are looking at in a focus group is combination products, which is tricky because you need to merge together qualification approaches for devices and drugs. We may have future recommendations in this area, but the working group is only in the planning stage.

What are the benefits of volunteering for an organization like the PQRI?

For me, the knowledge enrichment is very rewarding – and this comes from sharing information and listening to the experience of others. There is a growing diversity in the intended use for packaging and you can't experience everything yourself – you need to learn from others. For example, if you're working in a packaging company then it's important to hear opinions from drug manufacturers, and vice versa.

The world of E&L is dynamic. Simulation and modelling are emerging and it's possible that things may look very different five years from now. Even if we look back on the last two years, drug development has changed significantly – with new technologies and a move to digitalization. Having more data and being able to assess risks to products and patients early in pharmaceutical development, could lead to changes in E&L analysis.

THRESHOLDS AS DEFINED BY PQRI

- Safety Concern Threshold. The threshold below which a leachable would have a dose so low as to present negligible safety concerns from carcinogenic and noncarcinogenic toxic effects.
- Qualification Threshold. The threshold below which a given leachable is not considered for safety qualification (toxicological assessment) unless the leachable presents structure activity relationship (SAR) concerns.
- Analytical Evaluation Threshold. The threshold at or above which a chemist should begin to identify a particular leachable and/or extractable and report it for potential toxicological assessment.

Reference

1. *PQRI, "Safety Thresholds and Best Demonstrated Practices for Extractables and Leachables in Parenteral Drug Products (Intravenous, Subcutaneous, and Intramuscular)" (2022). Available at: www.pqri.org*

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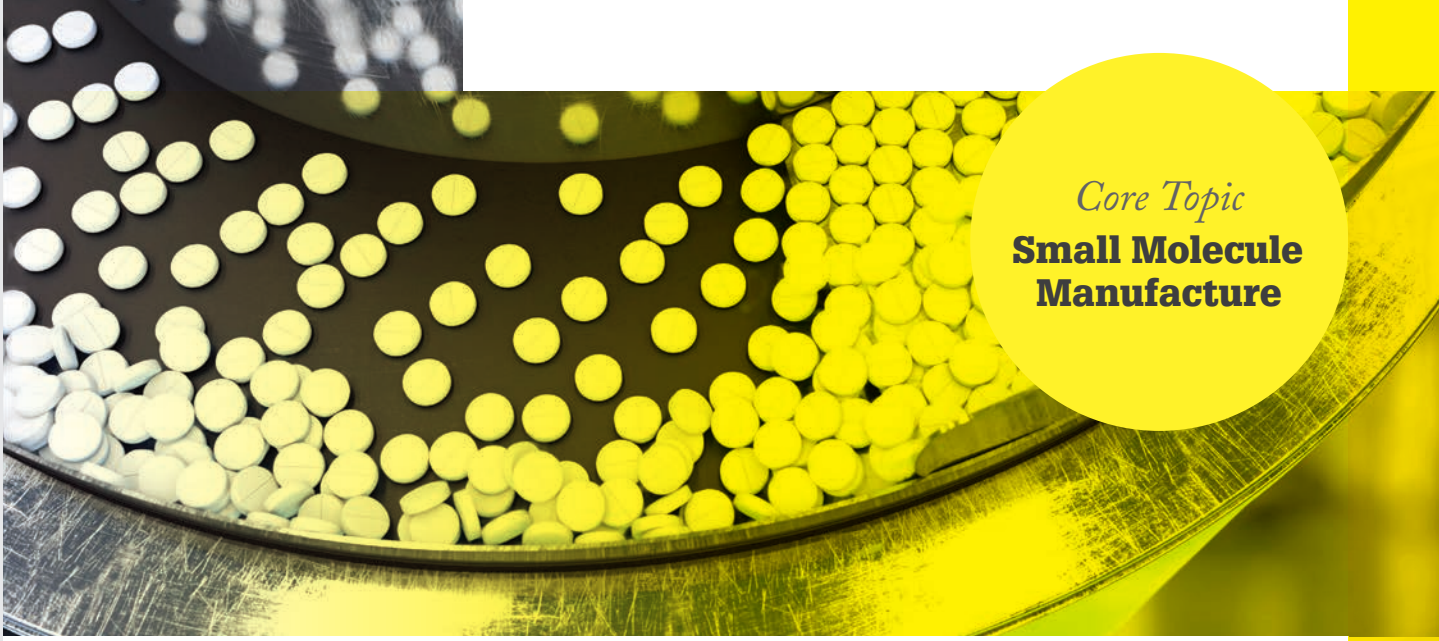


Core Topic

Small Molecule Manufacture

TEE is for timely. Could methods used for researching and developing new antibiotics in Europe be about to face a step change? According to a report from Charles River Associates, a Transferable Exclusivity Extension (TEE) is a "credible" and "workable" opportunity to accelerate European antibiotic research, which could prevent up to 400,000 deaths from antibiotic resistance in the EU each year. The report shows a significant reduction in the cost savings that come from implementing the TEE versus the expense of AMR-related healthcare costs. Commenting on the research, EFPIA Director General Nathalie Moll said in a statement: "We believe TEE will give Europe the tools it needs to protect patients."

Super compound. Every iteration of super villain augurs the arrival of an equal, but opposite, super hero. It stands to reason, then, that the MRSA superbug's nemesis should arrive in the form of a super compound – and it has, according to a team of researchers led by Maisem Laabei and Ian Blagbrough of the University of Bath, UK. Polyamine, a novel compound capable of destroying S. Aureus, has successfully completed in vitro tests against 10 different antibiotic-resistant strains. Laabei said: "This is important, as drugs that have the lowest minimum inhibitory concentration are likely to be more effective antimicrobial agents, and to be safer to the patient."

Brilliance and resilience. The Michael J Fox Foundation for Parkinson's Research has awarded $4.9 million to Copenhagen-based Muna Therapeutics to support preclinical research and development of small molecule potassium channel type 1.3 (Kv1.3) blockers to abrogate neuroinflammation. It is hoped that the therapeutic will achieve normalization of disease-associated microglial phenotypes, which will enhance neuroprotection and thereby preserve brain function and enhance resilience to neurodegenerative diseases. In a statement, Muna CSO Niels Plath said: "The studies will support ongoing medicinal chemistry and structural biology efforts, as well as extend understanding of the mechanism of Kv1.3 in microglial activation."

China in your hand. Shanghai-based CDMO WuXi STA has opened a high potency oral drug product manufacturing facility to meet growing demand. The facility is anticipated to produce around 400 million tablets and 200 million capsules annually. In addition, the company has announced plans for a US-based pharmaceutical manufacturing plant to add to a growing footprint of worldwide facilities, including a tablet and capsule site in Switzerland.

IN OTHER NEWS

The National Institute for Health Research in Sheffield, UK, awarded £12 million to accelerate scientific discoveries into new treatments for infection, immune disorders and more.

UCSF researchers identify ISRIB which recovers cognitive function in traumatic brain injury patients by blocking integrated molecular stress response.

LSU Health New Orleans uses NSC33353, a potential anti-tumor compound, in combination with doxorubicin with positive effects against triple-negative breast cancer.

Seeking to develop precision small molecule medicines through covalency, Matchpoint Therapeutics launches as a spin-out company from Stanford and Yale Universities.

The Insight Partners: "Global drug discovery services market expected to grow from $16 billion in 2021 to $32 billion by 2028 at a CAGR of 14.5 percent."

Getting Smarter with Small Molecule Discovery

The search for new small molecule therapeutics is becoming increasingly difficult as companies focus on more challenging targets. We asked Tom Mander, CEO of Domainex, about the need for new drug discovery technologies. Here's what he had to say...

When I started out in my career, we didn't have access to high-throughput screening technologies, combinatorial chemistry, or other techniques that we take for granted today in drug discovery. There was also far less structural information available. There's been an explosion of technology over the past few decades and it's been amazing to watch the evolution. We can now dispense nanolitre droplets of liquid using exquisite technologies, such as acoustic dispensing. There have also been incredible advances in confocal imaging; if there's a translocation event between the plasma membrane and nucleus, confocal imaging technologies can visualize it! And we also have access to human tissues, obtained with informed consent, being used in research to come up with better diagnostic tests and to test compounds for effects on human cells in a laboratory setting.

In the past, drug discovery didn't give us the option to test compounds using human-derived materials. These days, however, there is access to stem cells and diseased tissues (with informed consent) that allow us to look at targets in a human context in the laboratory setting. In other words, we have more techniques than ever before to help us find new small molecule drugs with disease-modifying potential.

But despite this, there is still an uncomfortably high attrition rate in the industry, and the costs of developing drugs continue to spiral. Clearly, we still have work to do. I think we need new technologies that can make the drug discovery process more predictive. Vast data sources now exist, like the Human Protein Atlas, and AI technologies are emerging to help us sort through data to find new medicines. But it's still a needle in a haystack. And some diseases are proving very difficult to find new treatments for, particularly CNS diseases like Parkinson's and Alzheimer's. With the aging populations, these diseases will only become greater burdens on society going forward. As an industry, we've not covered ourselves in glory when it comes to bringing new medicines forward for these challenging diseases.

INNOVATION AGAINST PARKINSON'S

In the full article, available on our website *(tmm.txp.to/tom-mander-discover)*, Mander looks back on his career in small molecules and shares his hopes for the future – including how small molecules may finally be able to provide a breakthrough in Parkinson's disease. Domainex announced an exciting small molecule drug discovery collaboration with Parkinson's UK earlier this year.

Mander says, "Specifically, Parkinson's UK approached us to work on a new project involving a membrane-bound target on microglial cells. The charity already had some chemical starting points and we are now working to optimize these by improving the pharmaceutical properties including potency selectivity, physical-chemical properties, pharmacokinetics and so on. We're going to run a screening cascade and we aim to deliver a pre-clinical drug candidate that could potentially slow the onset of Parkinson's disease. One key driver for the program is to discover molecules that can cross the blood-brain barrier to reach the site of action. The program could last up to two and half years and we've set technical milestones to reach along the way, so it will be a fascinating journey of discovery with the scientists at Parkinson's."

You Shouldn't Need a Spoonful of Sugar

If companies truly aim to achieve patient-centricity, they must embrace the importance of taste masking

By Amie Gehris, Technical Service Manager, DuPont Water Solutions

Let's be honest: the bitter taste that is present in many solid and dispersible tablets can be enough to put people off taking the drug at the required dose. There are many methods and technologies that can be used to improve the taste of medicine but even in 2022, the patient experience often seems to come as an afterthought – and aftertaste.

For oral dosages that are soluble or require the patient to keep them in the mouth for a prolonged period, the bitterness of the API can be overwhelming (note that we are programed as humans to be sensitive to bitter tastes as it indicates that something may be toxic).

Certain patients, especially geriatric and pediatric, often find it difficult to swallow solid tablets and capsules whole, meaning liquid and soluble formulations are a preferred delivery method. Unsurprisingly, taste for these products is key to patient compliance. We should also be aware that children are often more sensitive to bitterness than adults – and also far more likely to refuse medication! Should we care about the young and old? Well, around 34 percent of the world population is either aged under 14 or over 65 – that's a lot of people who could benefit from drug formulations that are easy to swallow and not bitter to taste…

You may already know that there are many ways that bitterness can be masked. The API can be coated, sweeteners or flavors can be used, resins and polymers can be added to the formulation… Each approach either overpowers the bitter flavor, reduces contact with taste buds, or delays the release of the API. With all of these options available, is it not surprising that so many formulators are still wedded to their traditional delivery formats?

So you're sold on taste masking. What's the best approach? Well, it really depends on the API used, the degree of bitterness, the final dosage form, manufacturing method, and the target patient population. The addition of sweeteners and flavors may not be suitable for certain patients, such as diabetics, as increased sugar intake can raise their blood sugar level, so film coating and the use of polymers and resins may be a more suitable approach.

Ion exchange resins (IER) – insoluble polymers that contain acidic or basic functional groups – are increasingly popular but not at all new to the industry; in fact, they've been used for many years to control the release of APIs. By binding an ionic API to an oppositely charged polymer – the IER – to generate insoluble "resinates," the API is not released into the mouth, and is masking its bitter taste. It later will release the API in the gastrointestinal track to produce its therapeutic effect. And as well as facilitating delayed release, they can also be used to create fast dissolving formulations, such as dispersible and orally disintegrating tablets where the API comes into direct contact with the taste receptors in the mouth but masks the bitter taste.

I'm passionate about treating taste as an important factor in the development of new drugs – especially when so many of the world's medicines take an oral dose form and we see a continued rise in aging populations. Do we really want higher rates of noncompliance, hindered therapeutic management, and unhappy patients? There is a clear market for liquid and soluble formulations with efficient taste masking – and it will improve patient outcomes.

De-Risking Your Sterile Manufacturing Program

Drug development program sponsors are increasingly looking to CDMOs to help reduce risk and push projects forward. With more than 40 years of experience, Alcami knows how to minimize risk at every single step of the development path.

Featuring Mike Babics, Vice President, Parenteral Services, at Alcami

What is your background?

I started my career working in the development and manufacture of retroviral proteins for HIV research soon after I finished my undergrad degree in biology at Wheaton College. This early experience in CMC sparked an interest in the parenteral development space within life sciences. I then pursued an MBA and following graduate school, Samuel Fleming, the founder of Decision Resources and father of a close friend, recommended the CDMO industry as way to experience first-hand the impressive range of technologies utilized in the life sciences. I've never looked back, and I'll always be grateful for Sam's advice.

It is an incredibly exciting time to be working in biopharmaceuticals and I would encourage anyone studying the health sciences to consider joining the CDMO industry. I feel privileged every day to work with such talented team members, while helping clients to bring ground-breaking products to patients all over the world.

Alcami has been a US-based sterile and solid dosage CDMO for over 40 years. I had the pleasure of working at Alcami with the current management team from 2010 to 2015, focusing on expanding Alcami's presence in the New England region. I re-joined the company in 2021 as a biologics and sterile manufacturing subject matter expert within the business development team. We have been focusing on expanding out our sterile manufacturing offerings from a single fill-finish line, which was already manufacturing over 25 commercial sterile liquid and lyophilized products, to six fill-finish lines, with the addition of five new isolator lines for filling vials, syringes, cartridges, and lyophilized products.

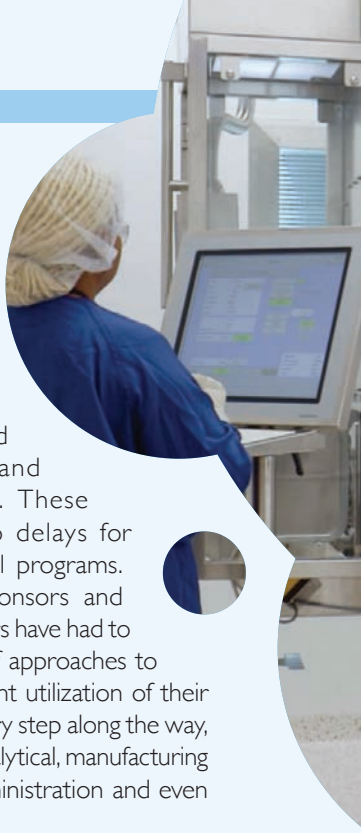
What are the big trends in sterile manufacturing?

The continued growth in demand for new therapies, combined with the decreased capacity and material constraints throughout the ramp up of COVID-19 vaccine manufacturing, led to an increased need for efficient utilization of the material generated by smaller scale GMP drug substance batches. Since 2020, a significant percentage of the industry's global resources, including facilities, consumables, raw materials, and operational staff, have been channelled into the pandemic response or impacted by supply chain and clinical challenges. These issues have led to delays for thousands of clinical programs. These program sponsors and their CDMO partners have had to utilize a multitude of approaches to maximize the efficient utilization of their GMP material at every step along the way, from formulation, analytical, manufacturing and into clinical administration and even commercial launch.

Another pressing topic for the industry is the revised EU GMP Annex 1, which was released with updated requirements for sterile drug manufacturing at the end of August 2022. The pharma industry has been given one year to reach compliance with the new Annex revision, and two years for lyophilization systems. Of particular interest is the regulatory expectation that barrier systems (or isolators) will officially be a default expectation for aseptic processing of any products intended to be administered in countries following EU guidelines.

How can risk be minimized in sterile manufacturing?

It is crucial for a CDMO to develop a comprehensive tech transfer process that allows for early identification and planning to properly prepare for and, therefore, mitigate the high-risk portions of a client's process. Having the right expertise, technologies, and facilities are also key. One example of how Alcami is helping to prevent risk in sterile manufacturing



alcami

can be found in our investment into our newest flagship fill-finish facility at our Morrisville, NC campus, just 10 minutes from the Raleigh airport. The facility was designed using the core principles of quality by design to ensure that it would meet its intended purpose as a parenteral filling facility in all aspects. We considered the physical layout, utilities, air handling, and material flow prior to the installation of new isolator technology, and we use single-use systems with flexible filling and minimal line loss.

Indeed, we are committed to continual investment in our facilities, staff training, and quality systems to minimize risk at every step of the development path for our clients' products. During the last two years, we have invested more than $150 million to ensure that we are leading the industry in implementing best practices throughout our US-based facilities. Alcami has invested in the gold standards of technology in all our facilities, including isolators, lyophilizers, formulation technologies, environmental monitoring, analytical equipment, and their supporting technologies.

This approach has been at the core of Alcami's multi-year expansions at all five of our US campuses, and it not only helps ensure the highest quality but also the greatest reduction of risk to the programs we are entrusted with.

"During the last two years, we have invested more than $150 million to ensure that we are leading the industry in implementing best practices throughout our US-based facilities."

And how is Alcami preparing for the future?

Since 2020, in anticipation of the recent revisions to Annex 1, Alcami has purchased and installed five new isolator fill finish lines, and three state-of-the art lyophilizers with automated loading and unloading technology. These investments, combined with recently completed expansions at all of our analytical labs, will allow Alcami and our clients to meet current and future regulatory requirements, and ensure that we can fulfill the growing demand for clinical and commercial injectable products being distributed to the global market from the US.

What are the benefits of outsourcing – with the right partner?

Put simply: reducing risk in a program. Sponsors look for CDMO partners that offer extensive formulation and analytical method development that can be smoothly transferred into non-GMP batches for toxicology material, and then eventually into GMP manufacturing and release.

But finding the right CDMO can be challenging. Industry consolidation from mergers and acquisitions has resulted in a smaller pool of CDMOs with relevant industry knowledge and a good regulatory track record of successful INDs, PAIs, and BLAs.

Is Alcami the right partner? Alcami has been providing drug development, manufacturing, and analytical expertise for over 40 years. During this time, we have worked with an incredible range of clients and products. We have comprehensive development and analytical capabilities, robust technical expertise, state-of-the-art technology, and a history of collaborating with our client's CMC, analytical and program management teams to meet program timelines. We are focused on being the CDMO of choice for formulation, analytical development and testing, manufacturing, stability, and long-term storage of clinical and commercial drug product for solid dosage and parenteral products.

NextGen

R&D pipeline
New technology
Future trends

The Grand Challenge: Oligonucleotides Under the Microscope

Though highly customizable and therapeutically relevant, manufacturing challenges could pose setbacks for the growth of the oligonucleotide drug market. How, if at all, can they be overcome?

When we think about the next big thing in pharmaceutical development, our minds often turn to cell and gene therapies. However, other emerging drug modalities could also play significant roles in the future pharmaceutical landscape. Among them are oligonucleotide-based therapeutics. Smaller than biopharmaceutical molecules but larger than the average small molecule, these therapeutic agents typically comprise up to 30 nucleotide bases and can be used to alter protein expression and treat disease.

Current manufacturing approaches rely on solid support-based synthesis, which is associated with efficiency and sustainability challenges. Alternatives will be needed if the industry aims to scale up the production of oligonucleotides. John Arthur, Director of the Medicines Manufacturing Innovation Centre, led by deep tech innovation organization CPI, explains how the organization's grand challenge project could help overcome the manufacturing issues.

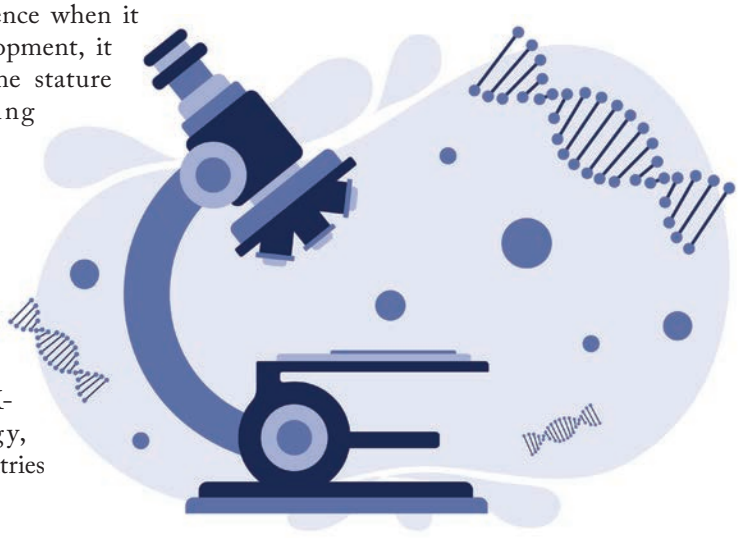
What is the Medicines Manufacturing Innovation Centre?

The top-level answer? It's a large cleanroom facility built to GMP standards, designed to foster a collaborative innovation culture and an industrially relevant environment. To provide more detail, the newly developed site, which is based in Glasgow, will be home to a series of "grand challenge" projects led by CPI that address key problems faced by the pharmaceutical industry. The first two challenges focus on issues in small molecule medicine development and manufacturing, but the third will explore how we can scale up and industrialize oligonucleotide technology.

This latter objective is important because, although the UK has a reputation for excellence when it comes to drug development, it doesn't have the same stature where manufacturing is involved.

What challenges does the UK face in pharmaceutical manufacture?

The UK doesn't have a great track record of industrialising UK-invented technology, unlike many other countries with similarly strong science innovation cultures. This issue became increasingly apparent when the pandemic hit. At this time, CPI was helping to industrialize a supply chain for an RNA vaccine. We were able to quickly mobilize our labs but, when we needed to scale-up development, international contacts with existing and robust manufacturing ecosystems were called upon to support the project. Though this was certainly positive (the resulting products went on to support COVID-19 prevention schemes), the information sharing



required meant that some intellectual property was lost.

Why is it important for you to build this infrastructure for oligonucleotides in particular?

Oligonucleotides are a relatively new drug modality, but development of – and interest in – these therapeutics is rapidly gaining momentum because of their ability to address a variety of diseases and reduce the amount of therapeutic intervention required. Where a patient may currently take a daily tablet to manage the symptoms of the disease they live with, oligonucleotide therapeutics could reduce this to a twice-yearly injection.

But current manufacturing practices lack the efficiency necessary to meet large-scale demand. Oligonucleotide therapeutics rely on short nucleic acid blocks to target specific sequences of mRNA and alter their capacity for gene expression. Although this makes them impressive therapeutic agents, companies could stand to benefit from an improved approach to manufacturing. Currently, each nucleotide base is added sequentially on a solid-phase resin to build desired products. Any waste is washed down the column with the reactants used, but after several reactions the overall efficiency and purity of the process is reduced, necessitating chromatographic purification to generate a viable medicine.

To overcome this, we examined how a move from solid-state to liquid-phase reactions could enhance the chemistry stages of processing. The liquid phase should allow us to create a small, soluble hub that the first base in the oligonucleotide sequence can attach to. From there, intermediate products and the final oligonucleotide can be manufactured in solution.

The oligonucleotide grand challenge is giving industry, government, and other pharmaceutical stakeholders in the UK

the opportunity to club together to look at this with a critical eye. For example, Exactmer, a spinout from Imperial College London and Queen Mary University of London, has some fantastic membrane and hub technology that help address the core issues of oligonucleotide manufacture described above. Novartis, AstraZeneca, Alnylam, and Innovate UK are providing the funding for the new technology industrialization and all the partners are collaborating to deliver a successful outcome.

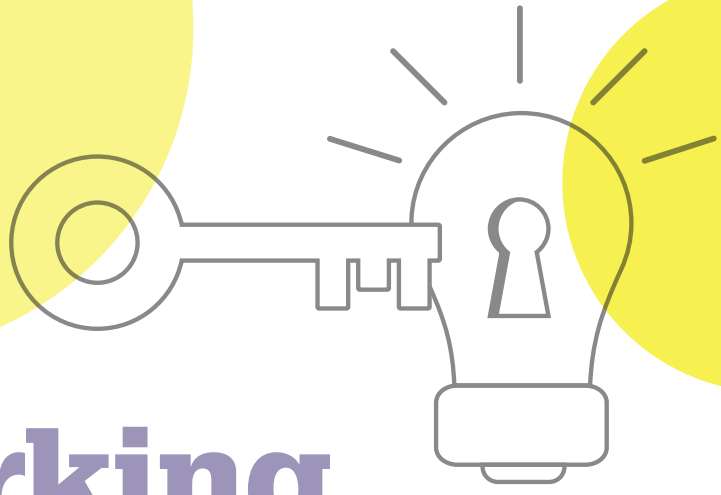
How else can manufacturing of oligonucleotides be improved?

Even if we improve the efficiency of chromatography, vast quantities of organic solvent (acetonitrile) are still needed during the process – and that's not good for the environment. We need to take steps to make oligonucleotide manufacturing greener; for example, replacing acetonitrile with water and moving toward biocatalysis rather than chemical processes.

Where will the field go next?

Though there are a number of oligonucleotide therapeutics on the market today, I believe we'll witness a massive increase within the next few years. The key roadblocks for these modalities remain linked to manufacturing and sustainability, but once they have been resolved, we may see a shift in the industry's reliance on them. Though many other interventions, such as cell and gene therapies, are increasing the available therapeutic treatment options, I think there's a gap in the market for oligonucleotides as they can be tailored to meet the broad and varied needs of patients worldwide.

There is a real buzz around them and I'm excited to see where the field will progress!



Business

Economic drivers
Emerging trends
Business strategies

Working Together to Unlock Innovation

How incumbent pharma can learn and benefit from disruptive entrepreneurs

By Chris Lord

The pharmaceutical industry has an innovation problem. Along my journey of filing more than 1,000 life sciences patents – and bringing some of those innovations profitably to market – I've discovered a few key ways that pharma can innovate.

First, a little background. I actually became a pharma innovator by accident, but I've always been interested in entrepreneurship and shaking things up with new approaches. In my second company, I had the UK's first alternative to nicotine replacement therapy (NRT) patches at the time: an e-cigarette. It was the first stop on my journey to try and get the world's one billion smokers (including me) to give up tobacco-filled cigarettes. Smoking-related illnesses were (and still are) a huge, solvable health problem, but, at the time, NRT patches were proving ineffective, with around 70 percent of smokers returning to cigarettes 90 days after temporarily quitting. My business partner and I set out to change that.

Though we expected to become technology entrepreneurs, we didn't foresee becoming pharma ones. The journey has been eye-opening. I've since created and sold two life sciences companies and also recently co-founded Prevayl, which embeds clinical-grade sensors into the fabric of sports clothing to help improve health outcomes.

Know your end game

For me, a great innovator sees the end game first. In the case of my vaping device and e-liquid businesses, it was a world without cigarettes. In another entrepreneur's case, such as Elon Musk, it might be transitioning successfully to sustainable energy or finding a way for humans to become a multi-planetary species. The point is that any good disruptor has a vision for what should change – and then tries to make it happen, no matter how difficult (or even impossible) it initially seems.

In pharma, as with many other sectors, incumbents are not always looking to an end game where a problem is solved; instead, they are typically protecting the bottom line – and seeing which existing products can be grown either via new audiences or new markets (or even new diseases). It's often about keeping shareholders happy and avoiding the risk of betting on something new.

An entrepreneur on the other hand, looks to achieve something world-changing and is happy to take risks to improve a product to achieve the vision.

When it comes to health innovation, there are so many challenges to solve. What about a world with 80 percent fewer cardio hospitalizations? That's the sort of end game goal I'd like to see from medical innovation. And medical innovation doesn't just mean innovating solely in new drugs or treatments, but innovating in how we find a solution.

But here's the important point:

disruptive entrepreneurs and incumbents can learn from one other. An incumbent can trust an entrepreneur to constantly develop bold new ideas, while the innovator can trust big market leaders to give their vision funding, scale, and even longevity.

Different mindsets

In a sector like life sciences, where specialists are crucial, it sounds counterintuitive to recommend more generalist thinkers.

Educational systems encourage us to focus on specialization from a relatively early age. For example, individual research scientists who become real experts in their particular field can still find it difficult to take a more holistic view of a given problem or challenge. For me, all too frequently this leads to a lack of joined-up thinking.

An entrepreneurial mindset, on the other hand, favors a more cross-discipline approach. While innovators do not necessarily have to master everything, they usually have a broad range of knowledge and know people with the expertise required should they not have it themselves – or, at the very least, have networks in place to help find someone who does.

Such a broad-based way of dealing with problems also gives entrepreneurs an awareness of the pieces they need to complete their "jigsaw puzzle." For example, someone without entrepreneurial flair may not be particularly cognisant of the value of social media for awareness-raising and sales generation purposes when launching a new product. On the other hand, an entrepreneur will undoubtedly understand the power of such networks – and they will know that they need to hire an expert if they do not possess the right skills. Because successful entrepreneurs are 100 percent committed to achieving their vision, they tend to be honest with self appraisal and quick to identify and fill the gaps in their own knowledge and skills – the puzzle pieces that must be provided by others.

Ultimately though, I believe the most vital components of an entrepreneurial attitude consist of a willingness (and ability) to question everything and the determination to find answers. In our pursuit of answers, we must zoom out to see the bigger picture (but also zoom in on the details). In a pharmaceutical context, zooming out means exploring the root cause of disease; for example, we could examine the role of nutrition or sanitation in the creation and maintenance of a healthy immune system and how this impacts overall human health.

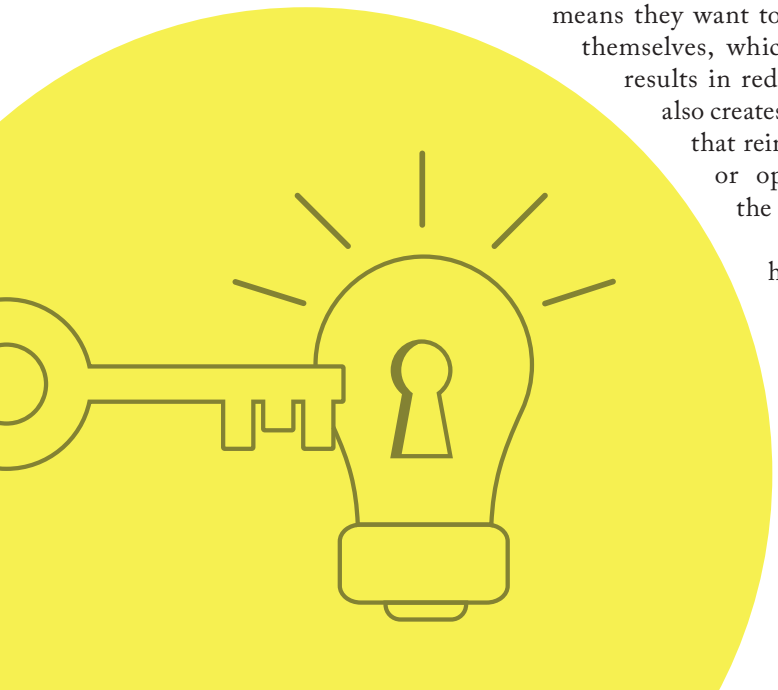
"I believe the most vital components of an entrepreneurial attitude consist of a willingness (and ability) to question everything and the determination to find answers."

The elephant in the room? Healthy people pose a threat to public companies

that make profits from sick people. Imagine a world, however, where stopping humans being ill in the first place becomes more profitable. In this win-win scenario, prioritizing the treatment of poor health causes – rather than symptoms of disease – would result in healthier people, less stress on healthcare systems, and more sustainable profits for pharma companies. With increased longevity and aging populations (according to the WHO, by 2030, 1 in 6 people in the world will be aged 60 years or over), this sort of prevention-instead-of-cure approach will be increasingly vital.

To some established companies, this shift in approach may sound threatening and radical, but it's gathering interest in certain entrepreneurial corners, which could lead to major disruptive innovations in healthcare. With the right product and market fit, you can find healthy profits from healthy people. More portable, wearable, ingestible, and implantable inventions are coming into the market to monitor health and fitness information, engage patients and their communities of caregivers, and deliver self-regulated therapies autonomously. And there are digital therapeutics to help deliver personalized preventive interventions; for example AI-powered apps using patient data, behavioral science, and gamification to drive adoption of healthy behaviors.

Having zoomed out, let's zoom in. In innovation, understanding the minutiae can be just as important as the bigger picture. I have personally rescued test results for a pharmaceutical e-liquid by spotting that clarity tests were being negatively influenced by the poor, overused, and badly scratched state of the inspector's safety glasses! The innovator zooms both in and out – oscillating between the two to find the answer. A public company CEO does not. To offer a simple analogy: there is a big difference between the person who invents the wheel and the person who keeps the wheel rotating.



"Contrast this with a highly diverse startup, where everyone is working backwards from a vision and openly discussing the best way to get there."

Avoiding the "madness of crowds"

Having sold businesses to large incumbents and having spent time in those public companies, I've witnessed first hand how groupthink can – and does – harm innovation.

CEOs see themselves as good, decent, and successful people because, more or less, they often are. And that means they want to hire people like themselves, which almost always results in reduced diversity. It also creates an echo chamber that reinforces the choice or option chosen by the CEO.

Fear also plays a huge role in holding innovation back in public companies. People try to avoid having a negative impact on their own career – so they may not openly disagree with the boss or propose something contradictory or risky. If employees do pluck up the courage to recommend something innovative, leaders want assurances that any risks will pay off, which stifles creativity. Almost every decision made in a public company is made only after considering and implementing an "ass-covering" option – perhaps a consumer survey or a published report to fall back on. The all-important bottom line and quarterly shareholder demands generate a risk- and innovation-averse culture from the top down.

Contrast this with a highly diverse startup, where everyone is working backwards from a vision and openly discussing the best way to get there. This culture is usually lively and, in my experience, even uncomfortable, but there is typically a reliance on understanding the evidence rather than simply following a leader's charisma.

I've been working with my business partner, David Newns, for almost two

decades, and I can say we've been on numerous horrendous startup-style roller coasters. But we have never argued. We have often disagreed and had contrary viewpoints, but we have never responded to a disagreement by digging in heels. Our responses to each other have always been open to the other's contradictory view. We'd ask each other, "Why not? What haven't I seen? How are you seeing it?" It's not about being nice to each other; we just know we must put our egos aside, respect the other's perspective, and insist on finding the right outcome or right answer. In a typical corporate "meeting," where everyone is focused on out-doing their counterpart, the right answer often becomes less important than personal outcomes.

Creativity can come from anywhere, so embedding innovation into company culture at every level is mission-critical. My business partner, David, strongly recommends that public company CEOs should hire entrepreneurs to make the value of creativity pervasive. I agree. Supporting these mavericks – and allowing them to take (managed) risks – can help bridge the innovation gap between disruptive startups and incumbents.

Share the financial burden

As a startup, paying for drug development is tough. If I'd known in advance that, on my mission to get smokers to give up cigarettes, I'd first have to pivot my technology startup into a medical device company and then into a pharmaceutical company, I may have quit before I began. It was a big mountain to climb – tens of thousands of pages for our submission to the UK's Medicines and Healthcare products Regulatory Agency, medical device testing, extensive lab facilities, a small army of specialists… I found myself at the helm of a huge multi-disciplinary undertaking.

As with any new medical product, we needed to commission a clinical trial and this, even with only 24 people, was set to cost – in 2012 money – close to $900,000. Like any strapped-for-cash startup, we tried to fund R&D organically via sales from a related business, but the cash flow required was unsustainable. Though the numbers involved might seem almost trivial to a large incumbent, they are extremely high for a two-year-old startup. So, rather than big pharma companies snapping up startups after the risky R&D has been done and the product is close to market-ready, could they come in earlier and help get the innovation to market faster?

I believe that entrepreneurs and big pharma CEOs can each offer the other something valuable. For me, entrepreneurs succeed or fail on solving problems worth solving, whereas big pharma companies succeed broadly by protecting their downside. By investing in startup R&D budgets rather than just buying the company and by bringing entrepreneurs into their own businesses to foster a culture of creativity, CEOs have the power to shape a world more capable of innovation – perhaps even a world that strives to create wellness rather than cure sickness.

D is for Decolonize

Sitting Down With… Luis Pizarro,
Executive Director, DNDi

What does leadership mean to you?
Sports works as an analogy. Some people would say you become the leader of a team by being its best scorer. Another school of thought says that the coach, who decides the team's strategy, is the leader. When I was young, I played a lot of basketball. In fact, I competed in the Chilean championships. Over time, I realized that I preferred coaching to scoring, and this came to inform my work in health.

How did you enter healthcare?
At 20 years old I moved from Chile to Europe to begin my medical studies. While in France, I was taught by people from Médecins Sans Frontières (MSF, or Doctors Without Borders), and I soon realized that I wanted to work in their field.

After my medical studies, I completed a Master's degree in Foreign Affairs, and just after that I was sent on my first field mission to support Niger's national HIV program. In time, my work turned to efforts toward strengthening the roots of access to healthcare in very resource-poor settings.

What are your views on the movement to decolonize global health?
If we are to talk about "decolonizing," we first need to determine what "colonization" means for us. Within the European empires of the past, the authorities sought to implement a colonial approach to public health. These efforts saw some successes, but they also made no effort to accomodate for local conditions. This colonial approach was the genesis of today's "global health," so the first thing we should do is reject that Eurocentric approach, and set up systems suited to local cultures.

Some of my colleagues would argue that we need to recognize that the way we behave and build our organizations today is deeply informed by a Western, white approach that offers insufficient space to alternative ideas, practices, and perspectives. At DNDi, I want to see how we can work on decolonizing R&D from the roots up – from talking to our colleagues who are running DNDi programs around the world, to ensuring that we are not bringing our solutions in a top-down, neocolonial approach.

What does DNDi need to achieve in the years ahead?
Across 20 years, DNDi has shown that pharma can operate outside of the for-profit model – we can rally the partners we need to run an alternative model. But now we need to prove that our model is sustainable. Right now, we run mostly on philanthropy and the generosity of wealthy nations' governments. We want to propose that R&D on neglected diseases is a common good. We need a new way of thinking and a new mode of governance to make this happen; for national and regional organizations to invest in R&D for their own populations.

And what about the challenges posed by climate change?
Conditions transmitted by mosquito bites are going to expand massively during the climate crisis, as is the number of climate refugees. Diseases that are currently isolated and concentrated in particular geographic spaces are going to spread. In fact, it's already happening.

Dengue is one such disease that will "benefit" from climate change. It hits the poor the hardest, since poverty makes one more susceptible to disease. Upon catching a neglected disease you may lose your job and will still have to pay for medication, and so you'll fall even deeper into poverty. It is a vicious cycle, and to address it we must work with both scientific and civil society. By engaging with national governments and also regional organizations such as the Pan American Health Organizations and the African Union, we can make our response to the coming crisis.

"If we are to talk about 'decolonizing,' we first need to determine what 'colonization' means for us."

Twenty years on, can you sum up why DNDi's mission is still relevant?
The two years of the COVID-19 pandemic that we endured highlighted the inequalities in access, capacity, research, drugs, and more facing our world. When a global emergency arises, we have seen that the international community is absolutely not ready to respond. In the face of a crisis it cannot deliver an equitable public health approach that treats access to the necessary care as a human right.

In light of that knowledge, we at DNDi need to not only continue our work as-is, but also commit to working on other areas such as HIV and pediatric treatments. We need to think alongside stakeholders about what can be done to continue producing drugs, bringing them to market, and ensuring that they are accessible and relevant for the people who need them.

We will also need to think about how R&D should look in the face of the next pandemic, and the new diseases to come. We need to consider how funds can be intelligently allocated. It is not good enough to simply sit and wait for the next crisis without establishing international solidarity.

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