SEPTEMBER / OCTOBER 2023 # 93

the Medicine Maker®

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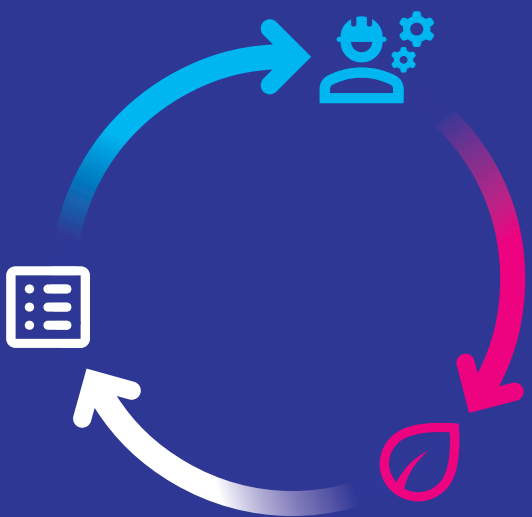

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The Backlash Against Women's Rights

As we move backwards in some regards, pharma companies could stand up for the other 50 percent – and still make a profit

The focus of this issue's cover feature is to celebrate women in the pharmaceutical industry – but also to look at some of the unique challenges that women face in rising to leadership roles (see page 18).

Some of you may be rolling your eyes as you read this – perhaps even muttering something about "woke culture." Here, I'll explain why it is important to carry on discussing the topic. Earlier this year, Human Rights Watch reported that gender disparities are worsening across the globe and that we are seeing a backlash against women's rights, including in the US, Poland, China, and South Korea (1). This concern is echoed by the United Nations (2): "Women human rights defenders have been facing serious challenges around the world driven by deep-rooted discrimination against women and stereotypes about their 'appropriate' role in society, intensified by rising fundamentalism, political populism, unchecked authoritarian rule and a focus on corporate profit."

Political issues aside, there is another fact highly relevant to an industry dedicated to improving health outcomes for patients. Women's health is chronically neglected when it comes to medicines. Case in point: the first oral drug treatment for postpartum depression (Sage Therapeutics' Zursuvae) was only approved by the FDA in August of this year. The year 2023 also saw the first FDA approval for an OTC contraceptive pill (Perrigo's norgestrel). Why has it taken this long?

In 2022, Neena Modi – then president of the British Medical Association – wrote about inequity in the UK (3): "Women fare more poorly compared with men in relation to disease prevalence, access to healthcare, and outcomes after treatment. For example, women are less likely than men to have a heart attack correctly diagnosed, and are more likely to experience poor mental health."

In the US, commentators suggest that doctors often dismiss women's pain (4).

Speaking to The Medicine Maker in 2022 (5), Sabrina Martucci Johnson, CEO at Daré Bioscience, claimed, "In dollars, only one percent of the approximated US$200 billion spent on healthcare research and development focuses on women's health." She also added that there is a prevailing attitude that women's health issues are "simply a part of being assigned female at birth."

There is a huge opportunity for the pharma industry here in terms of highly profitable drugs for unmet needs. If the pharma industry can successfully develop orphan drugs for rare diseases, it should be more than capable of creating drugs for conditions that specifically affect 50 percent of the world's population…

Stephanie Sutton
Editor

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1. *Human Rights Watch, "The Global Backlash Against Women's Rights," (2023). Available here*
2. *United Nations, "Gender equality and gender backlash," (2020). Available here*
3. *BMA, "Closing the gender health gap: the importance of a Women's health strategy," (2022). Available here*
4. *Harvard Health Blog, "Women and pain: Disparities in experience and treatment," (2017). Available here*
5. *The Medicine Maker, "A History of Missed Opportunity," (2022). Available here*

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first.lastname@texerepublishing.com

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Change of address info@themedicinemaker.com
Tracey Nicholls, The Medicine Maker, Texere Publishing Limited, Booths Park 1, Chelford Road, Knutsford, Cheshire, WA16 8GS, UK

General enquiries
www.texerepublishing.com | info@themedicinemaker.com
+44 (0) 1565 745 200 | sales@themedicinemaker.com

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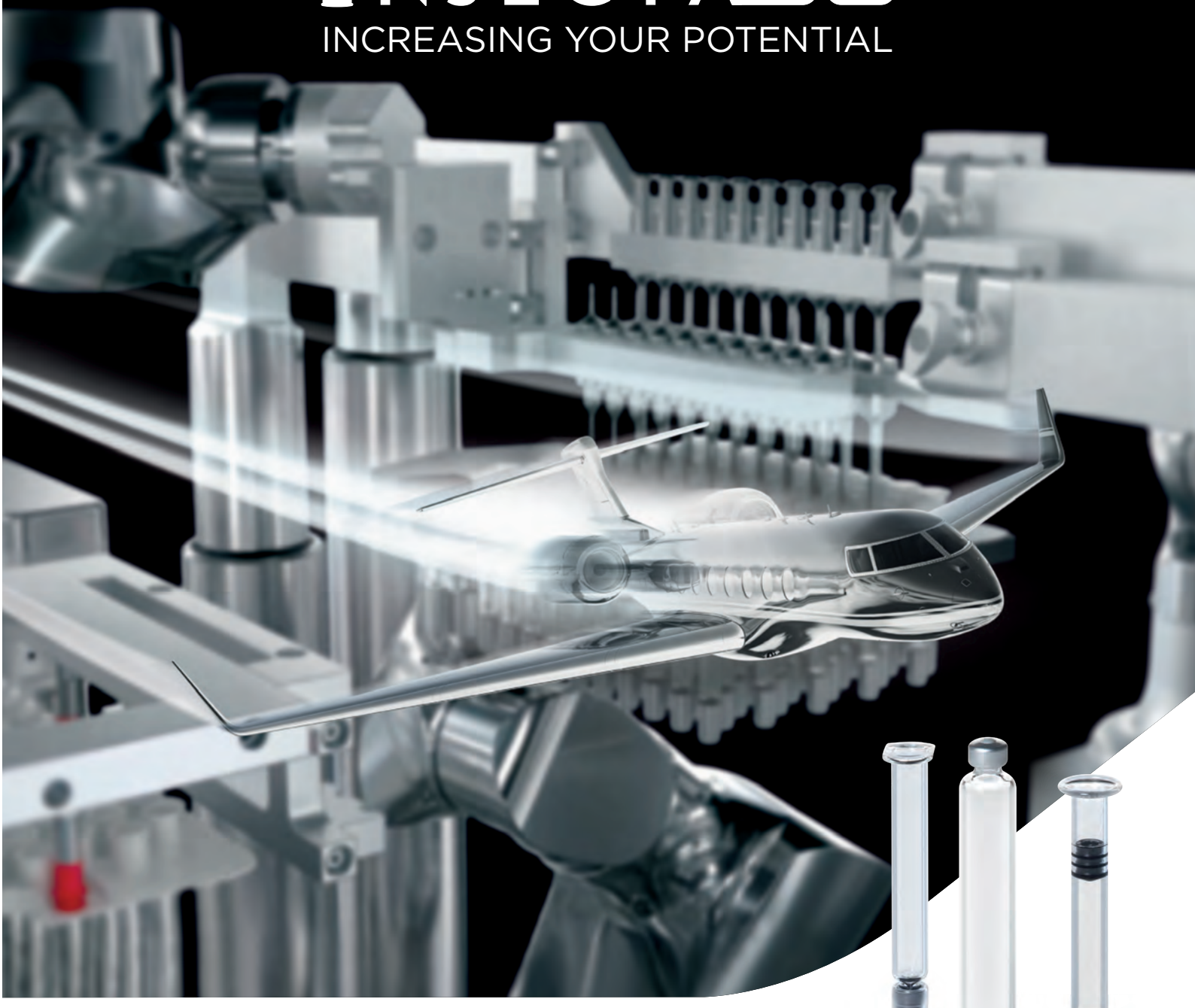

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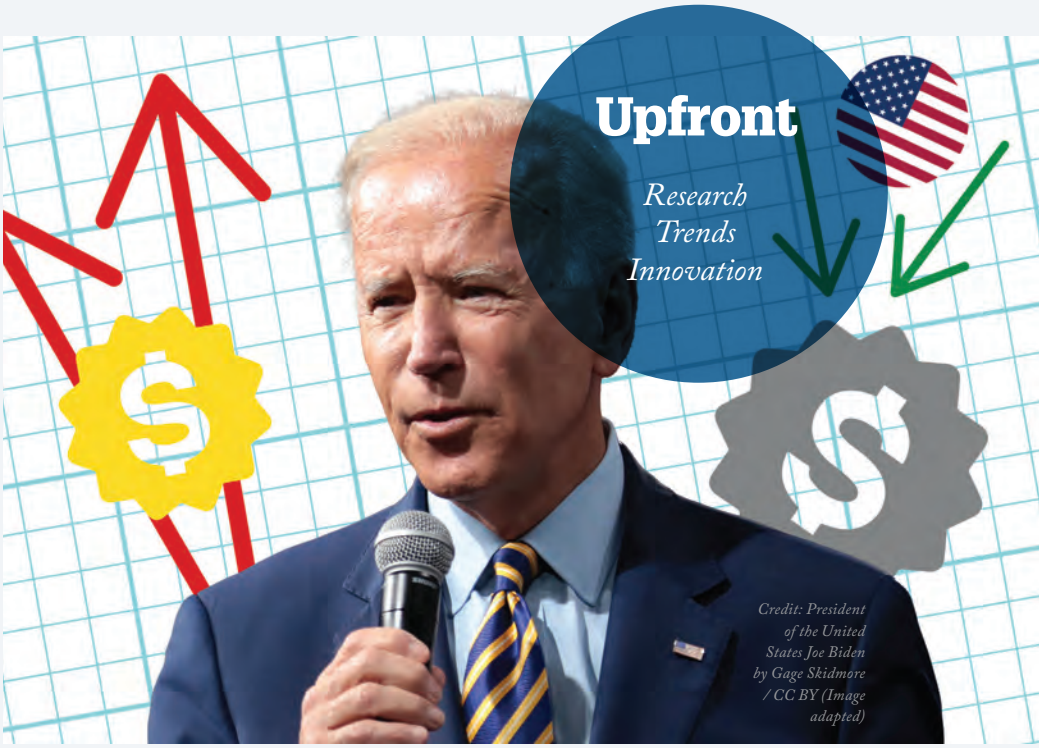


Credit: President of the United States Joe Biden by Gage Skidmore / CC BY (Image adapted)

The Inflation Reduction Row

More lawsuits launch as the US government reveals list of ten drugs for price controls

The Biden administration has published the first 10 drugs selected for the Medicare price negotiation process (see our infographic below) as part of the country's Inflation Reduction Act (IRA). The Biden administration claims that the program will save the federal government $160 billion over 10 years.

Patient advocacy organizations have celebrated, but industry stakeholders are on the other side of the fence. In a statement, PhRMA described the IRA as a "rushed process focused on short-term political gain rather than what is best for patients."

PhRMA is one of a handful of organizations (others include the Chamber of Commerce and big pharma companies) that have launched legal challenges to block the price negotiation program. All of the big pharma companies launching legal challenges have medicines included on the list. Two of the latest companies to launch lawsuits are Novartis and AstraZeneca.

In a statement, Novartis said: "The drug price-setting provisions in the IRA represent an unconstitutional taking of pharmaceutical manufacturers' private property and would impose excessive and crippling fines on any pharmaceutical company that refuses either to participate in the supposedly voluntary 'negotiations,' or to accept CMS's purported 'maximum fair price' (MFP) for a particular drug at the end. The provisions also force the company to endorse views with which it profoundly disagrees, in clear violation of Novartis' rights under the First Amendment."

However, some companies are backing away from the fight. For example, Astellas launched a lawsuit earlier this year but has now asked a court to dismiss it – perhaps because no Astellas medicines were included on the list of drugs for price negotiation…

The first hearings began in Ohio in mid-September and reportedly involved heated debate. Many expect the drug pricing program to ultimately go before the Supreme Court.

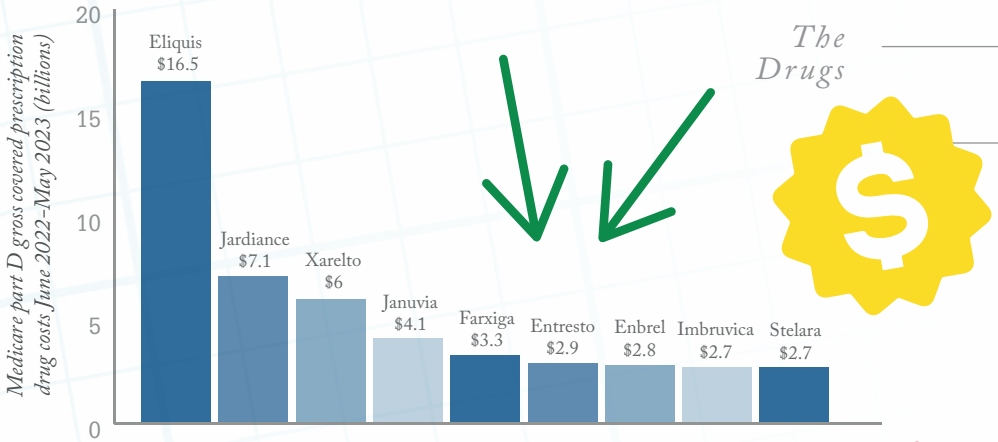
In a speech, Biden promised that the administration would "keep standing up to Big Pharma."

What are your thoughts on the IRA? Do you think it's good or bad for patients and innovation? If you have a view you'd like to share then please get in touch: stephanie.sutton@texerepublishing.com.

INFOGRAPHIC

The Battle of the Drug Prices

First ten drugs for Medicare drug price negotiation selected as part of the US Inflation Reduction Act



Source: Centers for Medicare & Medicaid Services

BLOGS-IN-BRIEF

One of our latest blog posts provided a breakdown of recent FDA warning letters. Here are some of the findings.

- Jamol Laboratories, based in Emerson, New Jersey, was caught manufacturing OTC products in insanitary conditions, including manufacturing in a corridor using a stained and debris covered fan surrounded by cardboard. The manufacturing space was described by the FDA as "uncontrolled," "poorly cleaned and maintained."
- Baxter received a warning letter for a facility in Ahmedabad, India. The main issues cited were inadequate investigations regarding endotoxin testing and an automated vial inspection system. "Your firm invalidated multiple endotoxin tests for finished products upon discovery of particulate matter in one or more wells used to perform the kinetic-turbidimetric assay (KTA) method," states the letter – also adding that a previous inspection had cited issues around endotoxin testing.
- Based in Erlanger, Kentucky, RenatilLabs was manufacturing a product (WJMAX) derived from human umbilical cord for allogeneic use. However, the company did not have a biologics license and the product had not been manufactured to cGMP. After stability testing revealed contamination with Staphylococcus epidermidis, the lot was not rejected and continued to be sold directly to physicians in the US.
- Centaur Pharmaceuticals in India received a warning letter for serious problems with contamination and cleaning. Residues containing multiple APIs from different products were identified on equipment. The letter added, "Your firm acknowledged that sections of the (b)(4), (b)(4), and (b)(4) have not been cleaned or examined for cleanliness since they were installed over 14 years ago." Centaur Pharmaceuticals manufactures products for Breckenridge Pharmaceutical, which issued a recall of numerous batches of medicines because of the inspection findings.

Read more at tmm.txp.to/fda-sept-2023

Meet an AI Model that Predicts Teratogenicity

How complex data analysis paired with artificial intelligence can help reveal additional causes of birth defects

When it comes to pharmaceuticals, predicting teratogenicity is challenging. In some cases, it is already known that certain drug classes are likely to affect DNA and cell division. In others, the potential risks to the fetus are unknown. Although drugs can be tested in animal models to understand if they cross the placental barrier, the findings may or may not translate to humans.

Scientists from the Icahn School of Medicine at Mount Sinai have created an artificial intelligence model that can predict which existing medicines – not currently classified as harmful – could lead to congenital disabilities (1). Their model – or "knowledge graph" – also has the potential to predict the involvement of pre-clinical compounds that may harm a developing fetus. The team concluded that drug developers should profile their compounds in cell lines to produce a signature of the genes that the new drug induces and represses.

Reference

1. *J E Evangelista, et al., "Toxicology knowledge graph for structural birth defects," Commun Med 3, 98 (2023). DOI: 10.1038/s43856-023-00329-2*

The Upcoming Key Dates

Sept 2024
Negotiated prices to be published

Jan 2026
New prices come into effect

2027
CMS will select up to 15 more drugs for negotiation

2028
An additional 15 drugs will be selected

2029 and beyond
Up to 20 more drugs for each year after will be selected

The Lawsuits

PhRMA
US Chamber of Commerce
Merck Sharp & Dohme
Novartis
AstraZeneca
J&J
Bristol Myers Squibb
Boehringer Ingelheim
Astellas (withdrawn in September)

The White House Response

"Although drug companies are attempting to block Medicare from being able to negotiate for better drug prices, we will not be deterred."

Exploring Alzheimer's in Women

Studying the link between Alzheimer's risk, estrogen levels, and menopausal status in women

Researchers from Rice University have won a three-year grant from the National Institutes of Health to look at how Alzheimer's risk, estrogen levels, and menopausal status interact with memory-related brain function and behavioral outcomes in women aged 35–80 (1).

According to the researchers, although the prevalence of Alzheimer's disease and the severity of symptoms is greater in females relative to males, the impact of estrogen decline with menopause is underexplored. Estrogen is known to have a large influence on cognition, with strong ties to memory function. Therefore, the loss of this neuroprotective sex hormone with menopause may contribute to increased risk for Alzheimer's disease in aging females.

"Historically, females have been viewed as more 'variable' when it comes to hormone fluctuations across the menstrual cycle. This was thought to make females less-reliable research subjects. However, given recent movements for the advancement of women's health research, the potential link between menopause and Alzheimer's disease is beginning to receive the attention it deserves," says Hannah Ballard, lead researcher of the work and Rice University postdoctoral fellow.

Research has also suggested that estrogen is important for protecting against the build-up of amyloid plaques – a neurological hallmark of Alzheimer's disease. And considering that estrogen loss occurs around the same timeframe that Alzheimer's disease pathology appears, perimenopause may represent a critical period for treatment interventions.

The ongoing study involves a memory task sensitive to age-related declines, in addition to structural, functional, and resting-state MRI to evaluate brain function and cognition over the course of the menopausal transition. Ballard says, "To assess estrogen levels and risk for Alzheimer's disease, we will collect a small saliva sample for hormone and genetic testing. This study will be performed in healthy adult females, spanning various stages from reproductive to postmenopausal years."

Reference

1. *S Clark, "NIH grant backs study focused on Alzheimer's in women," Rice University (2023).*

Celebrating People with Power

Who are the most influential and inspirational people in drug development and manufacturing? Nominations for The Medicine Maker Power List 2024 are now open!

When The Medicine Maker launched back in 2014, we had a clear mission in mind: to celebrate the people, processes, and vision that bring new drugs to market. After all, the development of new drugs draws on the talent, passion, and experience of a wide range of professionals. Essential to this mission is our annual Power List. The aim? To shine a spotlight on the influential and inspiring individuals contributing to the development and manufacture of new drugs within biopharmaceuticals, small molecules, and advanced therapies. We are now accepting nominations for 2024. Perhaps you want to nominate yourself or an esteemed colleague, mentor, or other inspirational individual. From CEOs to process engineers to benchtop scientists and academic blue skies thinkers, we accept nominations for people in big pharma, small pharma and everything in between – including CDMOs, technology companies, clinical trial organizations, regulators, and more. Nominations close on January 12, 2024 (https://themedicinemaker.com/awards/power-list/2024).

IMAGE OF THE MONTH

Nobel Winners

Katalin Karikó and Drew Weissman from the University of Pennsylvania's Perelman School of Medicine won the 2023 Nobel Prize in Medicine for their mRNA vaccine work. The Pfizer/BioNTech and Moderna COVID-19 vaccines use the technology developed by Karikó and Weissman.

Credit: Peggy Peterson Photography, courtesy Penn Medicine

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QUOTE of the month

"During the biggest public health crisis of our lifetimes, vaccine developers relied upon the discoveries by Dr. Weissman and Dr. Karikó, which saved innumerable lives and paved a path out of the pandemic."

J. Larry Jameson, executive vice president of the University of Pennsylvania for the Health System and Dean of the Perelman School of Medicine

FDA Approves First OTC Oral Contraceptive

Perrigo's Opill receives FDA approval following unanimous support from advisory committees

In what is considered by many to be a significant development for reproductive healthcare, the FDA has granted approval for Perrigo's Opill tablet for the country's first OTC oral contraceptive. Contrary to other estrogen- and progestin-based contraceptives, Opill only uses progestin, which means it can be used by people with a history of blood clotting or uncontrolled high blood pressure, according to the American College of Obstetricians and Gynecologists (1). The drug received unanimous support from the FDA's Nonprescription Drugs Advisory Committee and the Obstetrics, Reproductive and Urologic Drugs Advisory Committee underscored the benefits of OTC access outweighing any associated risks. Opill is expected to be available in store and online at leading retailers across the US in the first quarter of 2024.

Reference

1. *The American College of Obstetricians and Gynecologists, "Progestin-Only Hormonal Birth Control: Pill and Injection" (2023).*

Getting More from Your Buffer Management Strategy

By implementing MOTIV™ buffer management technology, Lonza has seen many gains, including saving space, greater efficiencies, and being more sustainable. We delve into the story behind the company's collaboration with Asahi Kasei Bioprocess America.

Featuring Matt Macknight, MSAT Manager at Lonza Biologics, Portsmouth, NH, and Chris Rombach, Senior Vice President of Sales and Marketing at Asahi Kasei Bioprocess America, Glenview, IL

When embarking on a facility expansion focusing on a state-of-the-art 4 X 6,000 L bioreactor multi-product manufacturing suite for complex products, Lonza had limited space for the overall manufacturing area. Buffer preparation and storage can take up a large footprint in a biopharma facility, so the company was keen to look at alternative options, which led them to Asahi Kasei Bioprocess America's (AKBA) MOTIV inline buffer formulation technology.

At Lonza, Matt Macknight developed the method of modelling and applying the MOTIV system across a wide variety of platforms – with help from his engineering partner Joe Conley. Together, they have collaborated with experts at AKBA to further refine how the technology is used. In this interview, Matt Macknight and Chris Rombach from AKBA discuss the benefits of updating buffer management strategies.

What benefits can new technologies bring to buffer management?

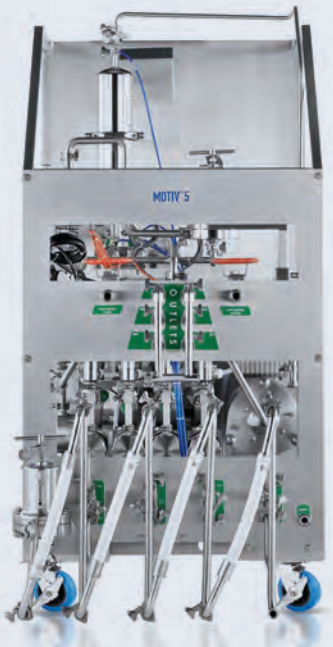
CR: Process buffers are ubiquitous in biopharma manufacturing. Often viewed as a background function, they are not always seen as a key focus area for improvement. However, as companies scale and diversify, material management and storage space become more pressing challenges. At the same time, sustainability is a focus for virtually all drug manufacturers today. All these trends make it a good time to review buffer management strategies.

MM: At Lonza, we've found that technologies like MOTIV allow us to do more with less. Biopharma processes use the same basic chemicals to purify API, but they are used in differing concentrations and different pH targets throughout each process. A traditional manufacturing suite making buffers the old-fashioned way requires a suitable facility footprint to house buffer preparation vessels and store formulated buffers. It also requires the staff to continuously replenish the formulated buffers according to the production schedule, in order to keep purification processes running.

We found that MOTIV removes a lot of these requirements. Instead of making formulated buffers, we can make either highly concentrated individual chemical concentrates that can be mixed with MOTIV to formulate on demand, or we can create a highly concentrated formulated buffer and dilute inline with water for injection. The system also reduces our use of plastic by eliminating the need for single-use bioprocess containers. In a traditional suite, we would be cycling through 50kL–100kL in single use containers for formulated buffer storage per batch. With MOTIV, we are now sending formulated solution directly to the chromatography and TFF systems, with no need for a break tank or containers.

What was the inspiration behind AKBA's MOTIV technology?

CR: AKBA has had buffer systems in the field since 2005 and we were awarded Bioprocess International's Technology of the Decade in 2012 for our inline buffer formulation (IBF™) systems. In recent years, there has been greater focus from industry on streamlining buffer prep, which inspired us to launch the MOTIV line in 2021, as a rebranding and product expansion of our IBF technology. We offer standard three and five pump designs, coupled with our patented "Pro Yield" mixing technology, and sensing and monitoring instruments to enable PAT.



We also respect that space can be a premium in today's facilities. We develop our systems to have the smallest feasible footprint possible. The fact that the system can also handle concentrated materials also saves space since companies don't need large storage tanks anymore.

MM: The space consideration was a huge focus for Lonza because we only had 10,000 L of storage space for chromatography and

TFF concentrates. I reviewed formulated buffer consumption in my asset and found that a typical process would require approximately 50,000 L to 100,000 L of formulated buffer per batch. With the MOTIV system, 10,000 L of storage space is enough, and the concentration is so high that we need only to use small amounts at a time. We have concentrates wherein a single make-up will get us eight production batches. Since we are not using bioprocess containers or a break tank, we only need a very limited number of buffer preparation vessels to supply the concentrates. Zero footprint is required to store chromatography and TFF formulated buffers, as well as reduced resources to maintain buffer supply. The production schedule also only needs ~1-2 buffer make-ups per 24-hour period when in campaign versus 10-12 in an equivalent asset without MOTIV.

Did Lonza face challenges when implementing the technology?

MM: We have manufactured eight different products in a GMP setting and over 50 unique formulations using the technology. The sheer volume of formulated buffer we have produced using the reduced footprint, equipment, and resource has been a huge advance in the manufacturing process. However, whenever you implement a new technology in a novel way, some challenges will arise.

For all our customers, we perform at-scale formulation testing. As a part of this process, we compare inline MOTIV pH and conductivity to offline using traditional instruments (considered the gold standard). The conductivity discrepancy between inline and offline instruments has been consistent at about 5-8 percent difference in every buffer formulation scenario. This difference is not an issue because conductivity ranges are typically at least +/-10 percent from target. When formulating to a specific conductivity, the system can very reliably maintain midpoint with very little fluctuation. We also incorporate the inline/offline discrepancy into our alarming strategy.

The pH inline/offline comparability has proven to be a little trickier. We have observed that above concentrations of about 50 mM of any chemical and with pH in the 5.5 to 7.5 range, the discrepancy between inline and offline is quite good at <0.05 units. However, at pH of ≤3.5 and/or a combined concentration of <50 mM of any chemical, the discrepancy is significantly higher and unacceptable for process control.

With pH discrepancies that are considered not comparable or acceptable, the solution can still be formulated by flow rate alone, not relying on inline pH measurement. As we are unable to trust inline pH measurements in these scenarios and unable to alarm for pH, we do more extensive at-scale testing with multiple source concentrates to prove that offline pH measurements are reliable and repeatable using flow rate alone. This has proven to be a very effective alternative control with this system. Ultimately, all scenarios are solvable using a mix of pH and conductivity control, flow control on its own, inline dilution, and inline formulation. As a CDMO that sees a wide variety of different process designs, having a system capable of all these control mechanisms is incredibly useful for us.

How are you collaborating to further enhance the technology?

MM: AKBA listened to our concerns. We provided them with a list of challenging formulations and AKBA has since built a development system. Our two teams are now collaborating to write a test protocol to recreate Lonza's observations, and to identify where on the molarity and pH spectrum the accuracy starts to decrease. Once confirmed, we will work together on system modifications or a new instrument that measures accurately in these scenarios.

CR: At AKBA, we build these systems and test them, and we know that they work well – but ultimately, we are not using them every day. Getting to know Matt, one of the key people using the equipment every day, gave us tremendous insight into the power of this technology and how it can be further refined. We're now recreating the issues that Matt has experienced in certain conditions. We believe that it all comes down to physics and chemistry in action. At low concentrations, we have observed that low levels of solute in the liquid may have an impact on the mixing and measurement by inline sensors. We continue to explore how the technology can be finetuned.

In this collaboration, we all recognize the importance of confidentiality, but it's great to see that Lonza had the open mind to share insights with us. In this industry, equipment providers and users need one another; we are all working towards the end goal of making medicines for patients, and to make manufacturing as easy and as repeatable as possible. It is a pleasure to collaborate with Lonza to improve upon what is already a very advanced technology.

In My View

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

Feeling the Heat

Transporting temperature-sensitive pharmaceuticals is only going to become more challenging as we face the realities of the climate crisis

By Nico Ros, Co-founder and CTO, SkyCell, Zürich, Switzerland

The summer of 2023 could very well be the hottest in history, and with increasing concerns around climate change we need to be prepared for further bouts of extremely hot weather. The global weather event, El Niño, and soaring temperatures in regions during the first half of 2023 and throughout the summer have heightened the urgency to address challenges posed by extreme temperatures and mitigate potential disruptions in pharmaceutical supply chains.

Transporting life-saving medicines using traditional methods, such as dry ice and styrofoam one-way boxes, falls short in ensuring product integrity and efficacy. Goods suspected of incurring a temperature excursion are simply consigned to waste, which can lead to shortages for patients. In my view, it's time to ride the transformative wave of temperature-controlled solutions and real-time data monitoring for pharmaceutical logistics.

In the pharmaceutical industry, failures in the supply cold chain alone cost the industry an estimated $35 billion a year, and much of this waste can be attributed to shortcomings in logistics. Temperature-controlled solutions are designed to withstand extreme external conditions and maintain precise temperature ranges required by specific products, including refrigeration, deep freezing, and ambient storage capabilities. This is done by incorporating insulation and advanced cooling systems.

With the advancement of technology, real-time data monitoring is also now possible. The integration of sensors and advanced tracking technologies within temperature-controlled containers enables companies to monitor critical operational parameters, such as temperature, humidity, and other vital indicators. This constant surveillance ensures that any deviations from optimal conditions are swiftly identified, allowing for immediate preventive actions. It enhances visibility, transparency, and accountability throughout the transportation process.

Even with well-controlled shipping strategies there can still be the risk of temperature deviations. Here, we can go a step further by combining simulation data (S data) with real-time operational data (O data).

S data plays a pivotal role in predicting and preventing potential issues before they occur. It enables proactive actions to be taken by solving problems before they occur. By predicting potential disruptions, identifying optimal shipping routes, and preventively addressing challenges that could arise during transit, simulation data can help ensure the integrity of pharmaceutical products. On the other hand, real-time O data provides immediate visibility into the ongoing status of shipments, allowing for real-time monitoring and quick reactions to any problems that occur.

However, the power of data goes beyond simulations and real-time monitoring. The intensifying impact of the hot weather demands innovative solutions for increased resilience and reduced risk. In this

"Even with well-controlled shipping strategies there can still be the risk of temperature deviations."

dynamic environment, the collection of upstream data directly from patients, creates a powerful feedback loop, revealing valuable insights into product performance. Armed with this knowledge, pharmaceutical companies can optimize their entire supply chain, fine-tuning processes to navigate the challenges of hot weather and enhance the delivery of life-saving medicines.

Ultimately, the power of data lies in its ability to drive continuous improvement and optimization throughout the entire supply chain and improve the overall patient experience. By using temperature-controlled solutions and leveraging real-time data monitoring, the industry can build a resilient ecosystem capable of navigating the hottest summers and unexpected disruptions.

Questions You Should Ask Your Cell Therapy Partners

Navigating the cell therapy partnership selection process can be complex. Here, I share the questions you should be asking to get it right

By Molly Mjolsness, Director of Client Experience and Transformation, Be The Match BioTherapies, MN, USA

As a cell and gene therapy manufacturer, some of the most important decisions you'll make revolve around selecting partners for clinical development and delivery, as well as commercial launch.

If a supplier cannot meet your needs, you may face delayed trials or a slow commercial product rollout, which costs time and money. Careful consideration during the supplier evaluation phase is critical – and that includes asking the right questions.

The cell and gene therapy industry is still young, but that doesn't mean you have to settle for working with partners with limited cell and gene therapy experience. Any potential partner should be able to prove in practice – not just in theory – that they've been successful in this environment before.

- As you evaluate partners, ask: Can you trust the teams assigned to deliver services to you?
- Do you have confidence they will move mountains to ensure your projects are delivered in the manner you expect?
- Does the partner have a proven track record of delivering on time and within budget?
- Are escalation pathways already set in such a manner that, when things go wrong (which they will), solutions are developed and deployed quickly?
- How will you justify your partner selection to senior executives and your board of directors?
- What evidence supports your choice between a known reputation

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and brand name recognition vs. a partner offering innovative new approaches that you think may better service your business?

When assessing the answers, don't just think about what you need today; picture where you are going so that you can select a partner who will meet your future needs too.

An ideal partner will have at the ready a list of technical challenges you are likely to face. They should be upfront about which of those technical challenges they are well suited to handle, which should be managed by your organization, and which are best to outsource to a different partner. Be vigilant in evaluating whether their technical plan achieves the outcomes you need within your timelines and budget while complying with relevant regulatory and quality requirements. When navigating both domestic and international markets, this can represent a significant body of work and you need a well thought-through and supported plan.

Recommended questions to ask:

- What types of issues or challenges have other clients experienced throughout their studies and commercial launches? What lessons learned can you share to help our organization avoid similar pitfalls?
- What qualification and validation data can you provide to support the quality and reliability of your core capabilities?
- As the utilization of our therapy grows, what mechanisms do you have in place to support scale? What barriers to scale exist today and what is on your technical roadmap to close those gaps?
- Where do you most often experience quality issues? What are your mitigation plans?

"A small startup may be able to offer exactly what you need, but may slow you down in other ways as they build out the fundamental elements of their product offering."

Experience in a partner is important, which often drives companies to large, well-established partners. But you must also consider how flexible they can be. They may not be able to customize their processes to meet your needs. At the other end of the spectrum, a small startup may be able to offer exactly what you need, but may slow you down in other ways as they build out the fundamental elements of their product offering. Balance is important. Try asking:

- How is the work we are proposing similar to and different from what you normally support?
- What are the costs and imelines associated with adapting standard processes to meet our unique needs?
- What are your standards and methods for qualifying and validating customizations?
- What risks or unintended consequences do we introduce by customizing our service offering?
- How have your standard offerings accelerated progress for clients? Are there common areas where your processes can get bogged down and are challenged to meet the needs of your clients? What improvements do you have planned in the next 12 months?

Cell and gene therapy is a rapidly changing industry. There will be surprises along the way and bumps in the road, and you will need to pivot quickly at times. A partner should work with you to build creative solutions to overcome the challenges you encounter.

When assessing potential partners and listening to their responses to your questions, ask yourself:

- Does this company's mission align with our company's mission?
- Do I trust this team? And if the individuals I'm working with now leave the organization, can I expect the same level of quality and service?
- Are incentives aligned to ensure this partner works as diligently as my own to achieve our key objectives? If not, how could we restructure agreements to drive mutually beneficial outcomes?
- Can I trust this company to partner closely in the most challenging of times so we can overcome obstacles and drive progress together?

Successful partnerships in cell and gene therapy happen when all parties move beyond the traditional supplier relationship. Market changes, regulatory changes, and scientific advancements push sponsors and partners to continuously evolve to make improvements and navigate hurdles. Ultimately, when partners are aligned on shared goals, they can overcome the challenges together.

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ECOnti: Sustainable Steps Towards Continuous Processes

How Tosoh Biosciences is contributing to a fascinating project on a mission to develop a continuous production process using *Escherichia coli*

The Austrian Research Promotion Agency (FFG) is helping make continuous biomanufacturing a reality by funding the ECOnti project – an ambitious initiative that aims to develop an accelerated, low ecological footprint manufacturing platform for continuous production of biotechnological products.

Austrian company enGenes Biotech – an expert on producing recombinant proteins in microbial expression systems – is leading the project but it also has assistance from other experts, including Tosoh Bioscience and the Institute of Bioprocess Science and Engineering (IBSE) at the University of Natural Resources and Applied Life Sciences (BOKU). In addition several SMEs (spin-offs from BOKU and the Technical University of Graz, e.g. companies Novasign, SimVantage, Qubicon) have joined the project and added expertise in process modelling and automation. Over the next two years, the ECOnti consortium of experts will develop a continuous production process using E. coli.

Here, Sebastian Thürmann, Product Manager for Multi-Column Chromatography at Tosoh Biosciences, and Rainer Hahn, Associate Professor at BOKU, Vienna, discuss the power of collaboration – and why this is such an important project.

What's the story behind ECOnti – and how did Tosoh Bioscience get involved?

RH: enGenes have a special strain of E. coli called enGenes-e$^{\times}$press, which enables growth-decoupled production of recombinant protein. As part of the project, we will be working with two fermenters; in the first fermenter, E. coli cells are grown, while in the second, the induction begins and the protein is produced – enabling continuous fermentation. enGenes has already proven that they can run the process for around 14 days.

enGenes is a spin-off from BOKU, which I have worked with before. Other BOKU-related companies are also involved, including Novasign (specialized in hybrid modeling of bioprocesses) and Qubicon (specialized in data management and system control). We formed a consortium to focus on continuous E. coli production, but we also needed a continuous chromatography system. In 2021, Tosoh Bioscience acquired Semba Biosciences, which is an innovator in multi-column chromatography (MCC). We asked them to join and now we have the perfect mix of experience needed to make the continuous production of E. coli a reality. The timeline of the project is only two years, but, as a group of rather small companies and academics, we can work with agility!

ST: With a continuous bioprocessing platform, the cells, feed, and consumables can all add to costs. The consortium aimed for fast and efficient continuous processing. Tosoh Bioscience was the ideal partner for the downstream processing part project, as our bench-top MCC system allows working with uniquely low flow rates - beyond the other benefits of MCC. In a nutshell, MCC can run continuously, intensifies the chromatography step, and reduces resin consumption by using multiple small columns rather than one large one. We are also contributing to the project by sharing our chromatography expertise in other aspects of the project, such as the development of a specific affinity chromatography media for process analytical technology.

What are the goals?

RH: If we are successful, we will have created the first continuous process for E. coli. Specifically, we are focused on developing a proof of principle that demonstrates the potential for three to four weeks of continuous production. This project is only possible because the enGenes E. coli strain can secrete the recombinant protein, which means we only need to separate biomass from the supernatant. Continuous cell separation can be done either by centrifugation or filtration. In our process, we ideally also want to add a control system that makes it possible to react during the chromatography step based on changes in fermentation titer so that the system can be maintained at the optimal steady state. Ultimately, we would like to have end-to-end process control.

If we had also required cell disintegration and removal of the debris then it would be more complicated to develop the process and technology – and I'm not even sure it would be possible to do these actions continuously.

TOSOH

ST: The goal is to create a fully developed, fully integrated, continuous, automatic upstream and downstream process that can work with batch sizes up to 10 L. We all hope to develop a process that offers significant advantages, such as a small footprint, reduced water consumption, lower energy consumption and CO_2 emissions, higher product yields, and enhanced process stability.

Mammalian-based upstream processes dominate current biopharma manufacturing technologies, but an end-to-end process for E. coli opens up a new and potentially more cost-effective option.

How can you ensure that the developed process will be truly sustainable?

RH: Today, there is pressure everywhere to make processes more sustainable in terms of the ecological footprint. At the same time, cost pressures continue to increase across the biopharma industry. Continuous processing can have advantages over batch production when it comes to environmental footprint. In the second year of our project, when the processes are more developed, we plan to perform economic and ecological modelling with the help of a postdoc graduate who is experienced in this area.

ST: Fortunately, socio-political pressures drive industries to search for more economical processes. A very straightforward way to accomplish that is by increasing efficiency. Efficiency means generating more product with lower resource consumption in a shorter time, a key feature of multi-column chromatography. As money savings are directly bound to consumable savings, I really hope that this financial-ecologic win-win situation will make MCC very attractive in the biopharma industry.

In ECOnti, we aim to reduce the amount of resin needed by 90 percent. My personal hope is that MCC is initially implemented in the production space to intensify chromatography. Once in use, the continuous working principle can serve as a seed towards fully integrated biomanufacturing on the DSP side, much like perfusion reactors are doing it for USP. Once users gather experience with continuously working units, they will more likely take a step towards integrated biomanufacturing, which will have a huge positive impact on the ecological footprint of the biopharma industry.

And sustainability is not only about environmental impact. Social equity is equally important, and improving the overall efficiency of biopharma processes will help reduce the cost of the target biopharmaceutical, hence allowing more patients to receive advanced therapies.

How is Tosoh continuing to innovate in the MCC instrument space?

ST: Our MCC instrument line is called Octave, and Octave BIO is our most comprehensive and versatile MCC system for process development and proof of concept – that's why the instrument is being used in ECOnti.

One of the major concerns MCC has been facing until now is the extra effort for the customer during the transition from batch to continuous chromatography. These can arise from regulatory challenges as well as from the actual process of method transfer. At Tosoh Bioscience, we focus on helping people to smoothen their innovation journey, and the first users of our MCC solution confirmed that we make the transfer from batch to MCC as easy as it gets by pairing versatile MCC instrumentation with intuitive software and dedicated consumables. This year we just introduced an MCC-dedicated column technology – SkillPak BIO – which allows very high flow rates and ensures low column-to-column variability, which is critical for MCC.

And our next focus is on facilitating the transition from method development to production. We will soon launch a moveable Skid-based process system for the GMP-manufacturing space, offering a single-use design for easier implementation and increased patient safety. To provide a similar holistic approach as with the process development solution, we will expand our pre-packed column product line with SkillPak PRO, which are manufactured under clean-room conditions and available in multiple MCC-specific dimensions. The easy software-guided method development and the seamless transfer from lab scale to production will enable our clients to develop and scale up their production quickly. I am convinced our holistic solution will have a significant impact in designing a more economical and ecological production of biopharmaceutics.

RH: To achieve the same performance, columns must be packed in exactly the same way. Why is this so important? Differences between individual columns prevent a steady state in the chromatography process. Tosoh really pays attention to this significant issue with its SkillPak approach.

Meet the Experts

Sebastian Thürmann

"I have dedicated my career to the field of liquid chromatography. My role at Tosoh Bioscience involves working with different technologies like columns, resins, and instrumentation, supporting diverse applications for our clients."

Rainer Hahn

"At BOKU, I mainly focus on biomolecule purification, including chromatography as well as the other unit operations involved. I do a lot of work at the small scale, but I've also been involved in scale up and modeling."

IS THAT THE SOUND OF BREAKING GLASS?

Women still struggle to reach leadership positions in all industries – including pharma. Now that we've acknowledged the issue, it's high time we overcame it.

We recently opened nominations for The Medicine Maker 2024 Power List (nominate here: themedicinemaker.com/awards/power-list/2024), which showcases the inspirational and influential players in drug development and manufacturing. We've published an annual Power List for nearly 10 years, but there is one glaring and recurring problem: the lack of nominations for women. Every year, the nominations we receive are heavily dominated by (white) men, leading to a final list also dominated by men.

There are, of course, many men doing fantastic work in the pharma industry – men who deserve to be recognized. But there are great women out there who also merit praise and recognition.

Is there a lack of women in STEM and the pharmaceutical industry? Some might say yes. At every major pharma event I have ever attended, I've noted a distinct imbalance.

Looking into the percentage of women that make up the pharma industry workforce has proven tricky. Some sources claim that over 60 percent of the pharma industry workforce is made up of women, but digging deeper I've found that this figure likely comes from a 2019 McKinsey report about women in the healthcare industry in North America (1), which is a little broader in remit than just the pharma industry (and also includes nurses, where 80 percent of the workforce is female). However, the report still has important findings; despite such a large percentage of women making up the workforce as a whole, only 26 percent of C-suite positions in healthcare are held by women (with women of color lagging behind white women). The lack of women in leadership positions is something that has been well documented in many industries. For example, in Silicon Valley companies, women hold only 11 percent of executive positions (2).

All of this suggests the existence of factors that prevent women from advancing their careers. Again, there is plenty of documentation in this area; women in the workplace face myriad challenges, including gender bias, lack of role models, and maintaining a work-life balance alongside the higher likelihood of taking on care responsibilities for children.

Here, we speak to women about their experiences in leadership. Yes, there are still issues, but, now more than ever, women are speaking up about the challenges – and looking to support others climbing the career ladder.

If you're interested in contributing to future features and articles about women in the pharmaceutical industry, please get in touch: stephanie.sutton@texerepublishing.com.

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HELLO – *From* WOMEN *in* PHARMA

The Women in Pharma network aims to inspire, empower and shape the pharma industry to better serve women. Meet the minds behind the mission.

By Miriam Kenrick and Sarah Sowerby

The idea for Women in Pharma (WiP) came about as the world was reawakening from COVID-19 lockdowns. We had planned a brunch in the spring London sunshine to catch up on the last two years.

Home alone with her two teenagers whilst leading her business through COVID-19, Kenrick had reinvented herself from stressed-out perimenopausal superwoman to yogi empowerment coach (a major overhaul to say the least!).

In parallel, Sowerby had transformed her wellbeing habits through an app called Second Nature, whilst running Wordbird with her husband (executive creative director, Andrew Nicholson) and being the best possible mother to a young son living with severe mental health issues.

There was a lot to catch up on. Amongst other topics, Sowerby talked about an exclusive female entrepreneur evening she had attended called Diamonds. The aim of the event was to create opportunities for female entrepreneurs and to provide a safe space for mentoring and encouragement. Initially, Sowerby had a large dose of imposter syndrome amongst the CBEs and OBEs, but when she heard the human stories of kitchen table businesses she realized that these people were just like her. Walking away inspired, she felt that this kind of networking event was needed in the pharmaceutical industry. If you can't see it, you can't be it. And we just don't see enough of the incredible women in our industry and the stories behind them.

Meanwhile, Kenrick had never thought about gender at work. She considered herself 'just a person,' and admits that she had always found it easier to be one of the lads, enjoying the banter and relative simplicity of male relationships. Sowerby had a similar mindset.

Though Sowerby had always valued strong female support networks, Kenrick admits that groups of women filled her with dread. She avoids hen-dos and has noted that the few women in leadership she does have experience with seem to always be sending emails late and on weekends, and traveling like crazy. Many are childless or have stay-at-home partners. Not everyone can relate to these types of women so more role models are needed, particularly for working mothers.

Empowering to unleash potential

We both feel we love working with "masculine energy." So if anyone thinks we're out to man bash – rest assured we love you!

However, we often feel as if many senior roles are announced out of the blue, with decisions made behind the scenes at the golf course, the bar, or a rugby match. This is something we have seen with our own eyes. For example, Kenrick was clueless how to navigate upwards after making it to director level. We need more stories that can inspire women so that we can learn how to break into the highest levels of leadership – and somehow do it without burning out.

As we ordered our second mimosa, the plan for WiP was already taking shape. Women need to do more than just inspire each other. There is significant evidence showing that we women tend to undervalue our achievements – focusing on what we could, or should, have done better. We often don't apply for jobs because we don't tick all the boxes. There are a catalogue of ways we hold ourselves back.

We need more than online modules of unconscious bias training to get more women into leadership. We need to let go of the disempowering beliefs and habits that we've unconsciously allowed to dictate our lives and stop trying to be "Superwomen." We need to learn how to prioritise our own wellbeing, create and manage boundaries, ask for and receive help, and start saying no.

We have a lifetime of cultural and societal expectations infused into our brains to be perfectionist people pleasers, helpers, carers, and, increasingly now, breadwinners. We need to help our women learn how to break the habits of a lifetime so that they can empower themselves, lead by example, and coach the next generation, so that they can learn to do this before they are in their 50s.

Shaking things up

The day after the mimosa brunch, Kenrick went to a bookshop (another post-COVID-19 thrill). By chance, she purchased "Invisible Women" by Caroline Criado-Perez. The book analyzes publicly available data through a female lens. From product and service design, such as cars and public transport planning (women are the majority of public transport users and they 'trip-chain' to the variety of places they need to go. Timetables and routes are designed by men for the work commuter), to the financial and legal worlds, to healthcare and medicine; the world is designed for – and in the interests of – men.

Since Aristotle, medicine has assumed all bodies are the same (except for reproductive parts), with females assumed to be just smaller males. In reality, every cell of our body is biologically gendered. The way our bodies work, what can go wrong, the diseases we get, the symptoms we experience, and the way treatments actually work (or not) can differ based on our biological gender, but the pharma industry has not focused on this.

Sowerby initially couldn't believe it. A lifetime of pharmaceutical grade evidence-based work made her very

skeptical, but then the Women's Health Strategy for England was published. Over 100,000 women contributed evidence to the government review on the health challenges faced by conditions that only affect women, and those that affect men and women equally. The findings were sad and deeply shocking.

Women are not taught about menstrual wellbeing. We are told that pain, erratic emotions, and heavy periods are just something we need to live with. We don't understand our own bodies and cycles. We might struggle to get pregnant, go through IVF, and lose babies – all of which is hidden from view. As we approach the peak of our careers, we go through perimenopause, which can be accompanied by brain fog, overheating, itching, becoming more anxious, not sleeping – the list goes on. And again everything is done in secret with partners unsure how to offer support.

We soldier on, until we are literally collapsing and are seen by a doctor. However, doctors are not taught about women's health either, and we are treated by a system often designed by (and for) men. Women are passed from pillar to post, struggling with health whilst keeping up all responsibilities in life. The treatments we are given often started out based on male rodents. Even when there is a split of genders in clinical studies, do we disaggregate it to look for differences? Do we always ask if a drug works differently in male and female bodies? Do we ask what the effect of the menstrual cycle is? Or the effect of hormonal contraception? Or the menopause?

#workinprogress #weignitepotential #weinspirepossibilities

Let us reiterate; none of this is about bashing men. It's about recognizing that we all need to ask more questions. When we care for women's health, everyone in society benefits.

The challenge is to change the system. This is something that WIP wants to do. To help companies ask more questions. To understand both male and females biologically and develop treatments accordingly. To encourage different conversations in areas such as R&D and regulation. To educate and empower everyone (whatever their gender) in the industry to make the necessary changes for the sake of our whole society.

Of course, neither of us know exactly what to do with

some of the biggest challenges, which is why we are building a community. A sisterhood perhaps; however, sisters have brothers too. All supporters of our mission are welcome! It's only together that we can solve these huge issues, and do it fast enough to help daughters, wives, if not grandmothers.

WiP has been going for over 12 months and we have almost 700 supporters in our LinkedIn group. We've run webinars, launched a podcast and run a couple of events in London (INSPIRE! and EMPOWER!). We have also launched some empowerment programs.

We are doing this alongside our day jobs, so we need other people to get involved to help run events and to expand our reach; people who can bring their own ideas of how we can inspire, empower, and shake up healthcare for women.

People ask us how we do all of the things we do. But the funny thing is how much energy it gives us. Having a bigger purpose and making a bigger positive impact is very energizing.

We hope you've enjoyed getting to meet us. We hope even more that you want to get involved. Most importantly we hope we've shaken you up a little and inspired you to make a bigger impact.

HOW *You* CAN GET INVOLVED

Join our email database: https://forms.gle/tEott6vi1749wTdW6

Join us on LinkedIn: Women in Pharma (WiP)

Try our Loose Women in Pharma podcast, which we're told people particularly enjoy. (All kinds of conversations happen here so be warned!). Search for Loose Women in Pharma on Apple podcasts.

DEMOCRATIZING HEALTHCARE (*in the* UK)

The disparities between women's healthcare, comparative to men, are clear. The "male as default" approach is seen in research, clinical trials, policies, and services that consistently prioritize male health. Today, we lack a clear understanding about conditions that only affect women (consider the menopause or postpartum depression) or how shared conditions affect men and women in different ways (1).

In March 2021, the UK government announced a call for evidence, which received nearly 100,000 responses, about female experiences within the healthcare system – from first appointments, discussion of treatment options, and follow up care. Common narratives from the report included difficulty accessing information on gender-specific health issues, extensive diagnosis periods, and, ultimately, 84 percent of respondents felt they weren't being listened to (2).

In response to the growing recognition of health needs and challenges faced by women, The Women's Health Strategy for England 2022 was developed. The aim? To address long standing gaps in women's healthcare and promote better health outcomes across the country within the next 10 years. The strategy covers a range of factors: increasing awareness of gender disparities in healthcare; addressing issues such as reproductive health, mental health, violence towards women; and a commitment to promoting women's rights and equality. It also builds on the UK's previous vision for the Women's Health Strategy for England, published in December 2021, which sought to establish new principles that could improve the health of women and reset how the health and care system listens to women.

But what is a plan without investment to back it? To date, the UK government has invested £127 million to increase and support the maternity and neonatal care capacity. Other improvements include banning virginity testing and hymenoplasty, and providing protections to domestic abuse victims through the Domestic Abuse Act 2021.

The government has also announced additional measures aimed towards boosting the health and wellbeing of women and girls. One of the top priorities is "one-stop shops" where women will be able to access everyday healthcare, such as family-planning services (such as coil fittings), prescriptions for HRT, or seeing a specialist about pelvic pain. Additional priorities include introducing compulsory women's health training for doctors and more cancer check-ups.

Let's hope this intersectional and equitable approach represents a new frontier for women's health worldwide.

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RUN *the* STEM WORLD

What actions can we take to help women and girls thrive in STEM fields?

By Patrice Jimerson, Associate Vice President of Diversity and Inclusion, Agilent Technologies, USA. This article was originally published in our sister publication, The Analytical Scientist.

Gender diversity in science, technology, engineering, and math (STEM) fields is a conversation we've been having for years. Most people claim to support gender equity, but diversity data doesn't reflect this notion. To resolve the challenges that hold women back from STEM fields, we need to use an intersectional lens that recognizes how other dimensions of identity affect women's experiences. It's time we take a step back to identify what's still driving the lack of representation – and how we can make tangible improvements.

Unconscious bias is by far the biggest roadblock in increasing the number of women in STEM fields. People know what the issues are and what they're supposed to do about them, but when the rubber meets the road, people still make prejudiced decisions based on their gut reactions.

Whether that manifests as a hiring manager thinking female candidates' family goals will interfere with their jobs or a woman being talked over by her male colleagues, this prejudiced behavior can deter women from pursuing STEM jobs. Unless people recognize their unconscious bias and are mindful of its effects, we won't make any progress.

The most prominent example of this signaling starts at an early age; if girls grow up without seeing women in STEM and leadership roles, it can subconsciously make them feel like they don't belong in those roles, either. However, when girls see people that represent them in the roles of CFO or vice president, it gives them hope of a successful future that isn't completely unattainable.

Another key obstacle is that many STEM-related industries don't have an actionable plan or consequences regarding gender diversity. Many companies aren't held accountable for lack of representation and fail to diversify their workforce. If a company's demographics go from 15 percent women one year to 12 percent women the next, what are the ramifications? Who reaps the benefits and who suffers the consequences?

I believe one of the reasons that gender equity continues to be an issue is because we've been thinking of gender in monolithic terms, when we should really be thinking about intersectionality. When you look at this issue across other dimensions of identity, it compounds the problem. Your race and socioeconomic background affect your access to education, your political power, and your pay equity. If your parents weren't in a STEM-related field, you're much less likely to choose that field yourself. Until we take all aspects of identity into consideration, we will continue to see low representation rates.

If we want to start dismantling the cultural and systemic barriers that hold women back from STEM fields, we need to address the problem as early as possible. It's imperative that girls of all ages understand that STEM careers are a viable option for them. We need to weave the love of science and math into the things that girls are interested in; sparking the interest of young women and girls, and continuing to nurture that interest throughout their careers. If this ideology is implemented across the world, we can broaden the pipeline of women entering STEM industries.

For example, the Agilent HBCU (Historically Black Colleges and Universities) sponsorship program provides crucial support to historically black institutes. This program ensures that black students have access to high-quality scientific equipment and STEM recruiting opportunities. If these resources are offered to other underfunded schools, we're likely to see more women from marginalized communities entering STEM fields.

To further push this ideology, we need to hold leaders accountable for upholding diversity. For example, encouraging business leaders to make an active effort to spend company money on diverse vendors or serving as a member or sponsor for underrepresented communities. If leaders aren't making these active decisions to improve gender equity, there must be consequences to stop this repeating behavior; for example, a negative impact on their ratings, bonus, or another pre-discussed metric. However, this shouldn't be an exception of performance, which relates to diversity and inclusion.

Another key element includes building awareness for those who aren't a part of these marginalized communities. By educating our male counterparts and those of other ethnic backgrounds of the barriers in place, we can work at breaking down walls and improving diversity and inclusion in the workplace. Without a diverse network, it is difficult to learn things that you wouldn't otherwise know. For example, have you ever listened to a woman with a disability talk about the challenges that have presented themselves during her career? To move the dial, we need men to make space for women to speak for themselves – and then to listen and understand their experiences.

Women are not monolithic. The reasons women leave their jobs vary greatly, and we need to slice and dice the data to understand those reasons before taking action to reduce it. In 2020, our data showed that women aren't willing to sacrifice their home lives for their work lives (1). Allowing women flexibility gives them the autonomy to create their own schedules, letting home life coincide with work.

The quality of interactions at work are also pushing women to leave jobs. Highly educated and experienced professionals are in demand. If women don't feel supported and empowered by managers or colleagues, they're willing to find alternative employment without having to make compromises. By creating more welcoming environments for women, people of color, the LGBTQIA+ community, and other marginalized dimensions of identity, we can improve the retention of women overall.

Often, when we talk about diversity and inclusion, it's as an add-on to the rest of the business, rather than an integrated policy. It needs to be part of the performance expectation and talent management. Diversity doesn't just happen. It's reflected by our customers, our partners, and our science. For it to be heard, it has to be purposeful.

Diversity can't be a one-and-done training. It needs to be experiential and dynamic. It needs to be reflected in what leaders say, do, and think about those involved in their business. It has to be fully integrated; until we do that, it will continue to be a challenge.

NOTES *on* DISPARITY *from* A FEMALE CEO

Do investors scrutinize CEOs more closely when they are women? It may not always be intentional, but research shows that subconscious bias does exist.

By Vineeta Tripathi, CEO and CSO, Vitarka Therapeutics

I have a vision for my company. I want us to be the market leader for non-viral drug delivery technology. We've already used synthetic biology to deliver therapeutic cargo into solid tumors. But I want our RNAi technology to target cells beyond solid tumors and deliver therapeutics to intracellular targets.

We raised our first investment within six months of setting up the company – and we are still raising investments today. This story ought to be nothing out of the ordinary – but there's an unfortunate reality we must consider: Life sciences companies with female founders often have a harder time securing funding.

Looking in the mirror

At Vitarka, the three biggest problems I initially faced were not connected to my identity as a woman. The first major problem lay in a perception among investors that Vitarka was "unrooted," simply because we weren't a university spin-out. Providing the level of confidence necessary to mitigate that perception was a challenge. The second problem was time – and how long it can take to progress from a commitment to invest to closing the deal. The third challenge was how to tell a compelling story about the problem we are solving and the technology we are developing.

Most of the venture capitalists that I have engaged with have looked beyond my gender and ethnicity. However, there have also been a small proportion of investors who made me realize that I am a brown, female start-up CEO – not just a start-up CEO. When I started out, I had never considered this. I never thought of myself as a brown female.

Fundraising made me realize both aspects of my existence! In the past, I had always thought "I am a CEO, period." I did not relate with being labeled as a "brown, female CEO founder," and indeed, across 20 years in the professional world I had never thought of myself in terms of gender or ethnicity. However, the fundraising journey made me look in the mirror and see that I am brown and I am female! Compared with my male counterparts, I feel that a small number of investors asked me more questions on all aspects of the business. For example, despite having letters of support from KOLs, some VCs asked to speak directly with the KOLs and thereafter declined the investment opportunity, offering only irrelevant feedback.

VCs should look at the competencies of the CEO, the track record of the team, the science, and the commercialization strategy; the gender or ethnicity of the person or people leading each of these functions should not be a consideration. I understand the need to have specialist funds supporting female founders. However, even within such funds, there is disparity – several are targeted towards "black female founders." So, what about other people of color, like South Asians? This problem can only be solved from the top level down.

Family, mentors, and society's expectations

My family is the foundation of everything I do. Be it my children patiently waiting while I present to VCs or my husband taking on the entire household responsibilities when I have a grant submission deadline, they share my vision of bringing RNA therapeutics to untreated and vulnerable patients. The support from Martino Picardo and Mayer Schreiber from Discovery Park Ventures in the UK as our first investors is unmatchable. Their belief in the team and the science has been truly empowering. They looked beyond my race and gender.

Martino joined me on this journey from day one. Having a chairperson who is also an excellent mentor with good emotional intelligence should be on every CEO's wish list. I remember my first meeting with Mayer, when he had already heard about Vitarka and checked out my track record. This level of modesty is commendable from an investor. After undergoing due diligence, Mayer committed the investment, saying that he believed in my ability to bring together a team and trusted that the science will work. Put together, he feels that these elements will make our company successful.

Some investors have doubted whether I can run a company while also being a mother. And I wondered what that meant. If a man can run a company while being a father, why is it different for a woman? But this mindset is deeply embedded in our society; women are expected to do it all. Initially, I used to apologize if my children jumped onto my lap during a late evening meeting. This used to make the investors on those calls slightly distracted, and doubt my abilities. And that's when I asked myself: Why apologize? I am being an excellent role model for my children; at the age of 3 and 7, they are already learning essential skills for entrepreneurship. And so, now, when my son comes onto my lap during a meeting, I say that a little learner has joined us as an apprentice. This change of tact shows the investors my confidence and leadership skills. Therefore, I would say that, before changing the societal mindset, female founders must first accept their own strengths as leaders and mothers.

Moving away from bias

How can we improve the investment process for female-founded companies? First, we need to stop identifying and labeling a female founder as a female. A founder is a founder, regardless of their gender or ethnicity. There has been a study called the Implicit Association Test – and I would encourage everyone reading this article to take the test. The test, featured in Malcolm Gladwell's book Blink, the Power of Thinking Without Thinking, demonstrates that, if interviewees are asked to fill in an equality and diversity form before an interview, it puts them at a disadvantage because they carry a subconscious bias towards their own gender and ethnicity. Likewise, the moment a founder is labeled as female, it is likely to put their pitch presentation at a disadvantage at a sub-conscious level.

This issue must be tackled at all levels – and there needs to be a cultural change that sees more women sitting at the board level, especially within investor teams. To date, about 95 percent of the investors that I have met and spoken with have been (white) men. There are several forums that discuss the problem of gender disparity in fundraising and the support required for female founders. Ironically, the organizers of such forums invite predominantly male founders or male investors to talk. In fact, forums discussing disparity for people of color still have white male speakers! We need change.

A good example from a VC perspective is SOSV's IndieBio program, which has more than 50 percent cohort companies with female founders and almost 30 percent with only female founders. I have not seen such a ratio anywhere else. At most investor showcases, there are usually only one or two female CEOs out of about 10.

Advice for women like me

My top advice is simple: Be who you are. Raising investment is about trust and your relationship with the investor, and that can only emerge from personal authenticity. There are no set societal rules that women need to follow. We don't need to be any more or less aggressive than men. We need only be ourselves.

To female founders who are also mothers like me, I have one specific message: Be confident and unapologetic. If your child crawls onto your lap during a meeting, there is no reason to apologize. Find pride in being a role model and demonstrating the leadership skills needed to manage the meeting and the child!

LEADERSHIP: KEEPING *the* FOCUS *on* INNOVATION

Life sciences is one of the most innovative industries in the world. What are the leadership skills required? Elke de Clerck, Global Science & Innovation Director at Rousselot, offers her perspective.

What helped you prepare for leadership?

My first manager told me something that has set the base for my views on leadership: "Your job is to make sure that we do not need you anymore in this position so you can progress quickly if you choose to – it is up to you to organize your future path."

It is my belief that encouraging people to find their own path to deliver success leads to a positive outcome for the entire team. I discuss with members of my team the priorities as they see them, rather than mapping out priorities on their behalf! I often share with my team the inspiring examples I've picked up from great managers I've had throughout my career.

Providing clear direction is essential, while encouraging individuals to determine their own path towards their end goal. Every team member contributes a valuable, unique perspective to every challenge. Bringing multi-disciplinary skills and expertise together allows us to unravel complex challenges and make decisions that determine the solutions we offer to our customers.

Are leaders born – or do you think leadership skills can be learned?

The question of whether leadership is innate or taught has been a topic of debate for some time. According to some experts, leadership is a combination of both innate qualities and skills that can be developed through education, training, mentorship, and experience.

Inherent qualities such as certain personality traits may give individuals a natural predisposition towards leadership. Traits such as self-confidence, empathy, communication skills, and the ability to inspire and motivate others can certainly help.

Ultimately, successful leadership often requires a combination of both intrinsic qualities and learned skills. While some individuals may have natural leadership qualities, anyone with a desire to be in a leadership role can improve their leadership abilities through continuous personal and professional development and, of course, having an effective manager or leader to support them!

What specific skills do leaders need to drive innovation?

Leaders need to be able to see opportunities and issues before they present themselves. It's not about a great spreadsheet or numbers. Instead, strategic discussions must probe whether something is interesting enough for a team to invest more time in.

All leaders must be able to facilitate effective communication and cooperation between people and teams so that different departments can work together synergistically.

Good leaders can think ahead of the curve, stay calm, and be flexible enough to provide an optimal work environment that encourages innovation.

How do you go about building a team that is geared towards innovation?

It's all about taking small steps; testing if a new product or solution works and adapting if necessary.

Our innovation team is a merger of four teams: the R&D, pilot, application, and science teams. To function optimally as one team, we have a common mission; everyone needs to understand what innovation looks like and what their roles are to deliver it. I believe that very interesting things happen at interfaces. For instance, the R&D team working with the science team. Our science team is focused on clinical studies, whereas the R&D team is more focused on developing products. They synergize well together and have made some exciting things happen!

I think freedom is also very important. Whenever I am recruiting, I make it clear that there is a lot of freedom and flexibility in the role, but there is also an expectation to deliver. Most people think this sounds great, but some people prefer more structure. Encouraging people to work towards goals or outputs without a structured guide can lead to excellent and interesting ideas, but it can also present a challenge.

To innovate, we need people

"TO INNOVATE, WE NEED PEOPLE TO THINK CONCEPTUALLY. FOR SOME PEOPLE, BEING ABLE TO DESIGN AND TALK ABOUT CONCEPTS, WITHOUT HARD PROOF, CAN BE A CHALLENGE."

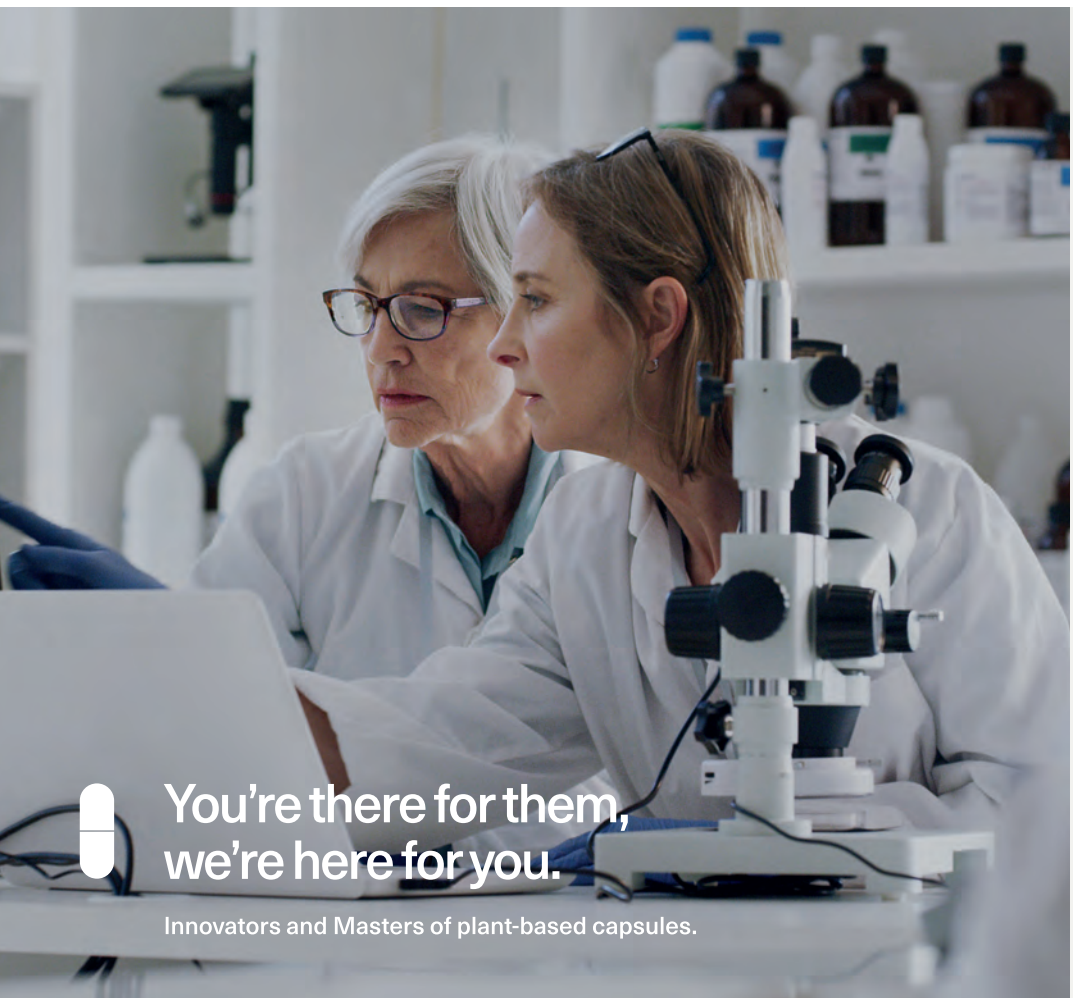
to think conceptually. For some people, being able to design and talk about concepts, without hard proof, can be a challenge. Some scientists are very black and white in their thinking, but innovation can be more of a grey area. With every study or research project, there are more questions. There are facts and data, but there will always be more unknowns to address. A good leader must be able to handle that difference and be able to explain the direction to non-conceptual thinkers.

Do you think women in science face additional obstacles compared to men?

Science is an excellent career choice for both men and women. I think it's incredibly important to create supportive work environments, promote diversity in leadership positions, and provide opportunities to share knowledge and expertise.

Combining motherhood and a steep career path was challenging, but I have not felt this has had a negative impact on my progression. I feel that having a family and juggling a career has helped me to be more empathetic and understanding, and to make clear, forward-thinking decisions. Being decisive while also taking a people-centric approach is incredibly helpful in business.

In my opinion, leadership is about giving purpose and direction to everyone so we can work together to achieve a clear goal.



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FOUR TIPS *for* LEADERSHIP

Each stage of every career comes with a different set of challenges. Early in Angela Osborne's career, she wanted to move forward fast but grew to understand that experience and learning were key to making a mark. Here, Osborne – founder and CEO of eXmoor Pharma – shares her top four career tips.

1. Experience is a learning curve

The questions I hear most when I mentor young people are "how do I get promoted fast?" and "how do I become CEO?" I was once like them; I was looking for my ideas to be taken seriously when I didn't yet have the experience to warrant that respect. Frustrating as it is, there's just no direct substitute for experience.

After moving from a biotech SME to a mature engineering company, I found myself pushing to be taken seriously in an environment dominated by older men. I had more self-confidence by then and I knew my point of view was valuable, but it sometimes took more effort than it should have to convince others of my credibility. However, that experience made me a stronger person and gave me the skill set to convince, persuade, and cajole to sell my ideas.

Developing support networks is also beneficial. By mid-career, I was fortunate to have senior-level support. I have since spoken to young women who finally get a seat at the table, then worry as they look around and realize it's all men. Imposter syndrome is a genuine challenge, but I like to remind these women that, generally speaking, any negative interactions they experience tend to be due to ignorance, not malice. It's important to try to move on.

Thankfully, I remain motivated to try to succeed in whatever I do. More recently, my challenges relate to leadership approaches. At eXmoor, we have been a relatively small organization for 15 years, but the time came in 2017 to build bigger. As we have transitioned, I've needed to redefine my role because it's impossible to be hands-on with everything! My goal now is to set a strategic direction. I leave it to my very capable team to perform. I'm lucky to have such great support.

2. Pick your battles

More experience has also taught me to choose my challenges more carefully. I'm competitive by nature, but I'm learning that sometimes you just need to let things go.

At my core, I am a positive person who generally expects things to turn out well. You could call that brave (or perhaps stupid!) but it's led to attempting – and succeeding – at what is commonly viewed as impossible. Although I have certainly learned from experience, I don't necessarily think I have handled each experience well. I remember trying to compete against colleagues with more experience but less competence (or so I thought!).

When I consider my initial, more confrontational approach, I think I should have found a way around people who I felt were holding me down, rather than going head-to-head. If I had handled things differently, then perhaps both of us would have benefited. I was in a hurry to get up the career ladder, but I realize now there are so many different routes – nobody has to follow a traditional, structured path. If I'd understood that, I might have put less pressure on myself. I remember being offered a ski season that I declined because I felt I needed to focus on my career and rush forward. There may have been missed opportunities.

3. Collaboration over competition

We played a game once during a management training program. The group devolved into two teams with both trying to outdo the other. Neither team won. And the group lost. Looking back, the obvious strategy was to maintain focus on the collaboration. We would have all succeeded if we had done that.

I reflect on this all the time in the cell and gene therapy manufacturing space. CDMOs have a nasty habit of disparaging each other, but the reality is that, for the sector to thrive, we need a good number of CDMOs to be successful or the entire industry won't work. Collaboration is required, not competition – it's better for patients if we all do well.

4. Come prepared to learn

Spend the early part of your career learning everything, getting as much experience as you can. It can sometimes be hard to recognize opportunities when they come along, but keep an eye out and be prepared. If you're given a moment in the spotlight in front of senior people, you're going to get noticed – for good or bad. I've seen young people thrive after approaching these interactions with enthusiasm and focus; I've seen others spend entire meetings scrolling through emails. It says a lot about you.

Know when to take opportunities. If you're put to work under someone with more experience, learn what you can and then move on.

Some young people ask me what the best place to start at an organization would be. I say it doesn't matter; everything has experience to give you. Once you're inside an organization, you can more easily look for other areas and move around.

When hiring young people with the prerequisite technical background, we value energy, enthusiasm, and the ability to think critically above all else. A willingness to learn and high energy must come across in an interview. Everything else can be taught.

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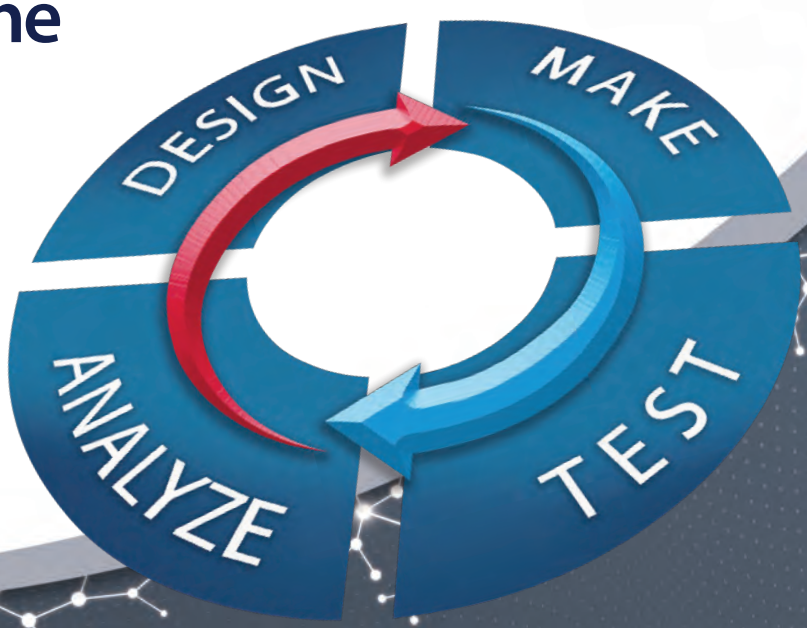

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The JOURNEY *of* FOUNDING *a* COMPANY

Lessons learned in starting up a company – and navigating an industry dominated by men

By Stacy Blain, Co-Founder and Chief Scientific Officer of Concarlo Therapeutics

I can't remember a time when I didn't want to be a scientist, and as a kid, I always imagined that I would have a lab in the back of my house. I was the kid who took the frog home at the end of the summer to continue dissecting it, irradiated fruitflys in the back of the classroom to see if I could change eye color in future generations, and built a model of the human body complete with veins and arteries. I wanted to know how things worked, so I asked a lot of questions.

My grandfather gave me a biography about Marie Curie when I was 7 years old. No one in my immediate family was a doctor or scientist, but I was fortunate to have exceptional science teachers from my earliest days. Ms. Hartsook was my first-grade science teacher, and she started me on this path. Dr. Crabtree, my high school science teacher – and the first person I met with a PhD – opened new aspirations for me. Before our introduction, I had only considered going to med school to do research. In high school, I realized I could get a PhD and do experiments all the time, and I went to Princeton because they had just opened a molecular biology department, distinct from the traditional evolution, ecology, and behaviour disciplines.

Concarlo's origins

After my PhD at Columbia, I went to Memorial Sloan-Kettering Cancer Center to finish my training, and worked in the lab of Dr. Joan Massague. Along with Drs Andrew Koff and Jim Roberts, he had just discovered this new protein, p27, and I essentially took up the mantle to continue working on this protein to figure out how it functioned. I have continued

working on this protein for the last 25 years and I became a faculty member at one of the state universities of New York. From the beginning, we had envisioned that if we could figure out how p27 regulated the kinases CDK2/4/6, we could harness that power to turn these kinases off in cancer. We sorted that out around 2013, and I started Concarlo in 2017. But while my entire career was probably headed towards the development of p27-targeting drugs, I hadn't focused on starting a company; I simply wanted to understand how p27 worked and how we could leverage its regulatory power.

A few things happened that really pushed me to start Concarlo Therapeutics and as a scientist, I was able to see that these forces were leading me in one direction. First, I submitted a large RO1 grant from my academic lab to the NIH in 2015, which was not funded. When I spoke to my program officer, he said that it was a great grant, but it was clear that I wanted to make a drug, which is something academics can't do. He suggested that I start a company, and get an SBIR grant to fund that work, and I applied to the NYC economic development corporation to get help with this.

Second, the tech transfer office at my university took me to a few meetings to meet with venture capitalists. I naively thought they would just fund my lab so I could continue studying the target and develop the drug. When they said that the tech was still too immature for their investment, they suggested that I start a company instead. I didn't know anything about the business of running a company, but I knew that I needed to find people that did and I found two co-founders. One was a 20-year veteran in the financial industry, who had decades of experience running and founding companies, and (importantly) raising money. The second was a fractional COO, who had started and operated companies for decades, albeit in a different industry. My university had an incubator on campus, and a recent graduate student from my lab joined. And so we began Concarlo.

Combatting cancer

Cancer is caused by uncontrolled cellular proliferation. The signals that normally regulate this process are controlled by a family of three kinases: CDK2, CDK4 and CDK6. In cancer, these kinases push the cancer cell into the proliferative phase. One of the goals in oncology for decades has been to turn these kinases off, but it is difficult because these three kinases look very similar to a large family of kinases. Most of the biotech industry's attempts to drug these three specifically have met with unacceptable levels of toxicity, by inhibiting targets in non-tumor cells or inhibiting the wrong target completely. Only CDK4/6 inhibitors have been approved by the FDA, but drug resistance is a common problem.

p27 is the master regulator that normally controls all three kinases, acting as a switch to turn them on and off. We believe that targeting p27 can help us to fight resistance, by inhibiting all three targets simultaneously, not leaving room for resistance to develop. p27 is not a traditional drug target because it is not a kinase nor a cell surface receptor, making it difficult to drug by small molecule kinase inhibitors or monoclonal antibodies. However, we followed nature's lead and co-opted the endogenous p27 inhibitor. Nature had already performed thousands of years of high throughput screening to find the best way to inhibit p27, forcing it to inhibit CDK2 and CDK4/6.

Concarlo is developing medicines that will convert p27 into its inhibitor mode to turn these three kinases off. Our approach will specifically inhibit only CDK2 and CDK4/6, producing a therapy with low toxicity. Since p27 targeting inhibits all three kinases, it will work in drug-resistant cells as well as treatment naïve cells. We have validated the p27 target as a way to inhibit CDK2 and CDK4/6 in numerous tumor types and animal models. We have developed our lead product, completed preliminary CMC, have assembled an amazing team and are ready to move this lead asset to the clinic in less than 2 years.

Our initial focus is metastatic, Ibrance-resistant breast cancer, but we will move on to other cancers driven by CDK2 (those that are a priori resistant to CDK4/6 inhibitors), such as ovarian. We will also look at cancers that involve mutations in the RAS/MAPK pathway, such as non-small lung cancer or melanoma.

The challenges of building a business

In 2017, there was little support for academics for start-up companies. In fact, most of my colleagues wondered why I was doing this. For me, however, staring Concarlo Therapeutics was the logical next step – both in my research and my personal evolution as a scientist.

If I had been in Boston or San Diego, it might have been easier, but New York was a very juvenile biotech ecosystem, with limited support. Today, New York is much more mature, with numerous incubators and accelerator programs, so I think the transition would be easier today, but academics will always face challenges. Academics do not have a rolodex filled with venture capitalists, so getting intros and raising money is difficult. Venture funds like to fund serial entrepreneurs or people they have backed in the past, which makes it difficult for anyone new to break into this funding space. p27 was a new target and our approach using a peptide was less traditional, so we had to do a lot of convincing.

Studies have shown that women-led companies yield better returns on investment, but women-led companies only receive ~2 percent of venture funding. Those two stats seem incongruous and might discourage women to start companies. Honestly, the latter would have discouraged me if I had known that! As a female CEO, I have a depressingly low chance of raising funding for my company. But that has to

"STEM IS STILL A MALE DOMINATED FIELD, ALTHOUGH THIS IS HOPEFULLY BEGINNING TO CHANGE."

change, and women need to continue to put themselves and their technologies out there. Find an accelerator or mentorship program to build a network of other women in the industry. Representation matters and learning from the talented women who have gone before will help during this journey.

Women in STEM

STEM is still a male dominated field, although this is hopefully beginning to change. There are more male faculty members in academia, more male members of pharma C-suites, and more male board members. However, we graduate nearly equal numbers of women and men with science PhDs, raising the question of where these talented and interested women go. I think we need to really figure out what the discouraging factors, policies, or systems are that make it difficult for women to stay in these industries.

Even for women like me – that have chosen to continue in this field, bias (both conscious and unconscious) – exists, and I have faced unnecessary obstacles during my path. For example, studies have shown that women that speak with more passive language tend to fare better in the workplace, get bigger promotions, and receive more funding and advancement, compared to those that speak confidently and with conviction (1). So to be successful, women tend to keep their mouths shut, making it difficult for bold women to gain tenure, move into C-suites, and on to boards.

Women and men enter science careers because they want to solve problems and be a part of solutions. My advice to women starting out is to follow your passion without going into this field blindly. Recognize that this is still a male dominated profession and be on the lookout for bias and obstacles. Find mentors that are familiar with the challenges associated with being a woman in a male-dominated profession. Make sure that you work in an environment where women are respected, promoted, valued, and encouraged. If you find yourself disrespected, speak up. This can be difficult as a junior person starting out, but if you don't stop that or call out the behavior at the outset, it will not disappear. You need to make sure that your gender does not become an obstacle.

Reference

1. *The New York Times, "Women Know Exactly What They're Doing When They Use Weak Language," (2023). Available here*

LEADING *with the* HEART

Up until March 2023, Sheila Mikhail was the CEO of AskBio, a company she co-founded with Jude Samulski to develop gene therapies. Now, acting in the capacity of advisor, Mikhail spends her time focussing on the challenge of battling cancer, and raising awareness of ongoing inequality for women in cancer screening and diagnosis. Here, she shares how to steer companies, employees, and herself through challenging times.

How did you keep employees motivated during difficult times?

We kept the focus on the patients and our mission. I always liked to tell our employees that we were revolutionaries changing the way that medicine is being practiced! Instead of treating the symptomology, we were trying to figure out what is causing the disease at the molecular level. From there, you can go in and fix it. I am still a firm believer that this is the future of medicine. Nobody benefits by just treating the symptoms, but if we can tweak whatever is wrong at the molecular level, and do that effectively and precisely, then the quality of life change will be amazing. We would be giving people back their lives, and giving children their childhood.

How important is it to have the right people around you in difficult situations?

It's incredibly important. Being a CEO is a very lonely place, and sometimes you're very uncertain about if you can achieve things, but you always have to project confidence, even at your lowest point. You don't want a bunch of yes people around you. You want people to challenge you and to help shape your ideas.

I love people who are committed and who work passionately. It's so much fun to work with people who are trying to do breakthrough science and genuinely achieve something new. Those people are dynamic and incredible. When you reach for the stars, maybe you won't get that far, but you'll get a lot further than if you set the expectations low. I've been very fortunate to have worked with people who are pioneers in their fields; people with big vision and who have stretched and pushed me to get gene therapies into the clinic for pathway diseases.

How important is it for CEOs to juxtapose altruism and philanthropy with business?

It is extremely important. Jude Samulski was approached by parents from all over the world who had kids with ultra rare diseases. It is very difficult for these patients and their parents to get attention from anyone in the for-profit sector. We find that our technology at AskBio works extremely well for many of these diseases with single-gene defects. If you can just replace the defective gene with a therapeutic gene, it works extremely well.

We believed that these children should not be left behind. Although we couldn't make the business case, we formed a non-profit, Columbus Children's Foundation (CCF), to focus on developing gene therapies for children with ultra rare diseases. We focused first on amino acid decarboxylase deficiency, which is an incredibly devastating neurological disease where children essentially end up strapped into a chair. They can't lift their heads. They can't talk, or use their hands, or feed themselves. They were treated with our therapeutic and, a year later, they are talking, walking, and feeding themselves. I have videos of kids skiing, dancing, and going to school. I've met some of these kids and it really makes you realize that every life is valuable.

But when you look at the numbers, you can't make a business case to go after that disease. It's really unfortunate because you're refusing to help because of an inadequate return on investment. I've seen how devastating disease impacts families. It's very stressful. We shouldn't think in macro, and dehumanize what we're doing. We have to think about everyone's potential. They are on this Earth and if we can make their quality of life better and allow them to make their contributions, then it is extremely valuable. If you're in possession of a technology that can make the blind see and make the deaf hear, you have an obligation to unleash that technology.

How did your career change earlier this year?

I stepped down as CEO of AskBio earlier this year because I was diagnosed with bilateral breast cancer. I was very surprised because I went for mammograms every year. They missed two sizable tumors. I've had a lot to I've had a lot to learn since then. been working to understand a very reputable institution (Duke University) missed the tumors, and I've been learning about cancer and cancer treatment as I navigate the options that I have. I've learned a lot about the flaws of breast cancer screening and I have spent my time educating other women by working with the legislature in North Carolina, and at the federal level, to pass laws that mandate insurance coverage or supplemental screening because, unfortunately, in my case (and many other cases), the doctors follow insurance coverage as the standard of care rather than looking at the patient's needs. Convincing insurance companies to expand coverage is not easy.

My tumors were found in time, so I have pretty good outcomes, but the whole process has been enlightening. I had to fight to get the proper screening and I was told that my insurance wouldn't cover it when I pushed for a chest CT.

Now I'm advocating for women because if I had to struggle this hard to get diagnosed, then God help other women. This is an example of equitable access. I'm doing my part to try to make changes in talking to and educating women, but it's always about insurance. You can cure disease by giving women the right screening tool for their breast type.

I've been trying to make something good from my experience and help others. Everything happens for a reason. I was the first in my family to go to college and I've always been driven by all the opportunities that came my way, as well as how I can help others along the way. A lot of people are not so fortunate. I have a big voice; I have opportunities, and I have resources, so I will apply those where I can to help others.

What are your hopes and expectations for the future of advanced medicine?

I'd like to see more diseases treated at the molecular level rather than just treating symptomology. Gene and cell therapy has it right: fix, rather than ameliorate, the problem.

I'd like to see more preventative measures using cell and gene therapy to prevent disease from occurring. It's also important to broaden access and affordability by driving down the manufacturing costs. I want to make sure people around the world get what they need. Part of this challenge is about having compassion. It cannot always be about return on investment.

When you lead with your heart, happen. I always tell people not to think about returns as return on money invested. Instead, think about the number of lives positively impacted. Guess what? It's a pretty good measure for both buyers and for returns.

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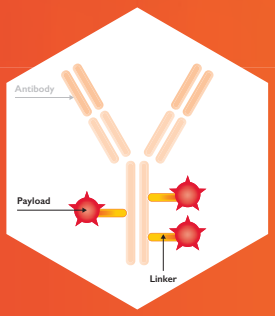

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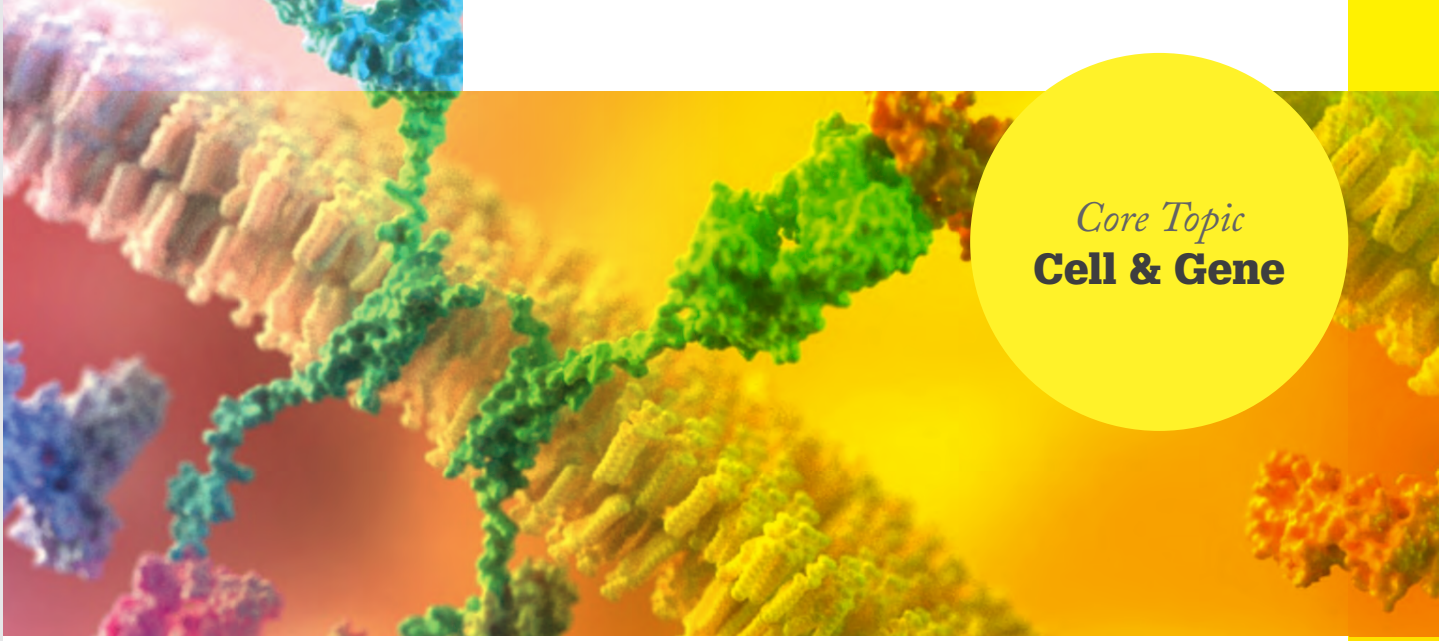

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Core Topic
Cell & Gene

Eliminating RNA viruses. Plasticell, the Cell and Gene Therapy Catapult, and Imperial College London have been awarded £800,000 to develop and manufacture allogeneic iPSC derived immunotherapies. Yen Choo, Associate Professor of Stem Cell Science and Regenerative Medicine in Singapore's Lee Kong Chian School of Medicine and the founder of Plasticell, said, "NK cells efficiently attack malignancies in an allogeneic setting – the next generation of iPSC-derived NK cell-based immunotherapies will disrupt the standard of care in hard-to-treat cancers. These highly engineered allogeneic immunotherapies are generally expected to surpass current autologous products in terms of their cost-effectiveness, safety and efficacy."

Go ape. Researchers from the UK's University of Sheffield have used mesenchymal stem cells to treat osteoarthritis – the most common form of arthritis – in a gorilla for the first time. The team carried out a comprehensive assessment of the gorilla's major joints and used the stem cells to treat alterations in the left hip and knee joints. Now, the researchers want to extend their efforts into a preclinical program to test their technologies for the development of a similar stem cell treatment in human patients.

MSCs against Alzheimer's. In other news about mesenchymal stem cells; Iran-based researchers recently assessed the dose-dependent therapeutic response of mesenchymal stem cells against Alzheimer's disease in a rat model. In the investigation, they demonstrated the ability of the cells to reduce neuropathological symptoms and promote the recovery of behavioral disorders. They believe that mesenchymal stem cells may effectively reduce the disease phenotype in the early stages, and exert neuroprotective and neurorestorative effects through paracrine mechanisms and neuroregulatory molecules. The team also found that the therapeutic response is attenuated when the dosage is increased.

Funding the future. Bristol Myers Squibb has donated nearly $1 million to Drexel University's School of Biomedical Engineering, Science and Health Systems in Philadelphia for the development and training of students looking to pursue careers in cell and gene therapy. The funding will form the basis of a new cell and gene therapy technology, engineering, analytics, manufacturing, and science academic program called CGT-TEAMS. "By empowering these bright minds, we're solidifying a pipeline of students who can help drive innovations across the fields of cell and gene therapy," said Wendy Clemens, vice president of Early Development Program Lead, Oncology at Bristol Myers Squibb and chair for the BMS STEM Council.

IN OTHER NEWS

Penn Medicine and Children's Hospital of Philadelphia receive $26 million grant from NIH to develop gene therapies for rare newborn genetic diseases

AGC Biologics announces capacity update at Longmont facility, with 30,000 square feet of added space and three new grade B cell therapy suites

Aldevron, Jennifer Doudna, and Innovative Genomics Institute collaborate on in vivo CRISPR therapies for neurologic diseases including Huntington's disease and ALS

First bladder cancer patient successfully dosed with intravesical gene therapy Adstiladrin (nadofaragene firadenovec-vncg) developed by Ferring Pharmaceuticals

Bruker signs agreement to acquire PhenomeX in all-cash transaction to gain access to multiple single-cell analysis platforms

Planes, Trains, and Autologous Therapies

The potential of the cell and gene therapies sector depends – partially – on the expertise of the transport and logistics partners that complement it

By Sumukhi Sreevatsan, General Manager, IMAPAC, Singapore

Train element by Kabelleger / David Gubler / CC BY (Image adapted)

The biopharma industry has seen exponential progress in the science of cell and gene therapy in recent years. Through my own work, through the accounts of our clients, and across the newspapers, I have seen more and more stories about lives changed and individuals cured by revolutionary therapies that would not have been possible 20 years ago. Earlier this year, a 19-month-old child became the first person in the UK to have her life saved by the gene-based therapy, Libmeldy. In 2019, a UK-based 11-year-old was the first child to receive CAR-T cell therapy that has been proven to fight against leukemia.

Conditions and diseases previously believed to be terminal are now being overcome by the great advances made in cell and gene therapies. As the field progresses, however, the biopharmaceutical industry will need to keep pace with its development in all aspects of manufacturing, distribution, logistics, and administration. Key to seeing cell and gene reach their full potential will be the advancement of cold chain systems.

In my view, the sensitive nature of cell and gene material has constrained both research and treatments. Though cold chain systems have been well established in the dissemination of pharmaceutical and biologic products, their application for cell and gene remains in the early stages.

Cell and gene material is highly susceptible to metabolic decline. When left for a protracted period of time at unsuitable temperatures, the quality of the material declines irreparably and the product ceases to be usable. This problem is particularly true in the case of cell material. Genes are inherently more stable and can therefore be transported with much the same systems as conventional pharmaceuticals and biologicals, but

"The cell and gene therapy supply chain and logistics market is expected to be worth $3.12 billion by 2031."

cells require much lower temperatures to retain their treatment value over periods of distribution. By storing and transporting this cell material at cryogenic temperatures, the product can remain, almost indefinitely, in a metabolically inactive state, and thereby invulnerable to any related decline.

The importance of cold chain systems to cell and gene therapies ramps up with the increasingly widespread distribution of the therapies. Cell and gene material has the power to endure over short periods of time without the need for significant temperature reduction. In such short-term cases, products can be refrigerated before use in treatment or research. As cell and gene therapy expands, however, and as demand for products becomes more widespread globally, the biopharmaceutical sector will need to bolster existing channels and build new means of transporting material across vast distances – from the manufacturing lab to the hospital.

We must strive to deliver cell and gene products as widely as possible. Without sufficient cold chain systems in place, these therapies are reliant on a "just-in-time" method of delivery – meaning that cell and gene material needs to reach the intended patient within a strict time frame. For the biopharmaceutical clients that I work with, this limitation means that the manufacturing of products is tightly bound to the schedule for their administration. If that schedule changes – because the treatment is canceled or postponed by the hospital for example – the cell or gene material will no longer reach the patient within the necessary timeframe, and the product must be discarded.

From speaking with our biopharmaceutical clients and reading reports on the sector's progress, it has become increasingly clear to me that the industry needs coordinated efforts and investment into developing a more robust cold chain system for cell and gene therapies. Fortunately, progress is being made. In fact, the cell and gene therapy supply chain and logistics market is expected to be worth $3.12 billion by 2031 – but this promising trajectory of funding and production will need to continue.

Cell and gene therapies bring with them great promise but also, like many medical innovations, some grand challenges. Addressing the sector's logistical challenges is fundamental to the future of the field; we must work together, if we are to take the next big step forward in realizing this great promise across the globe.



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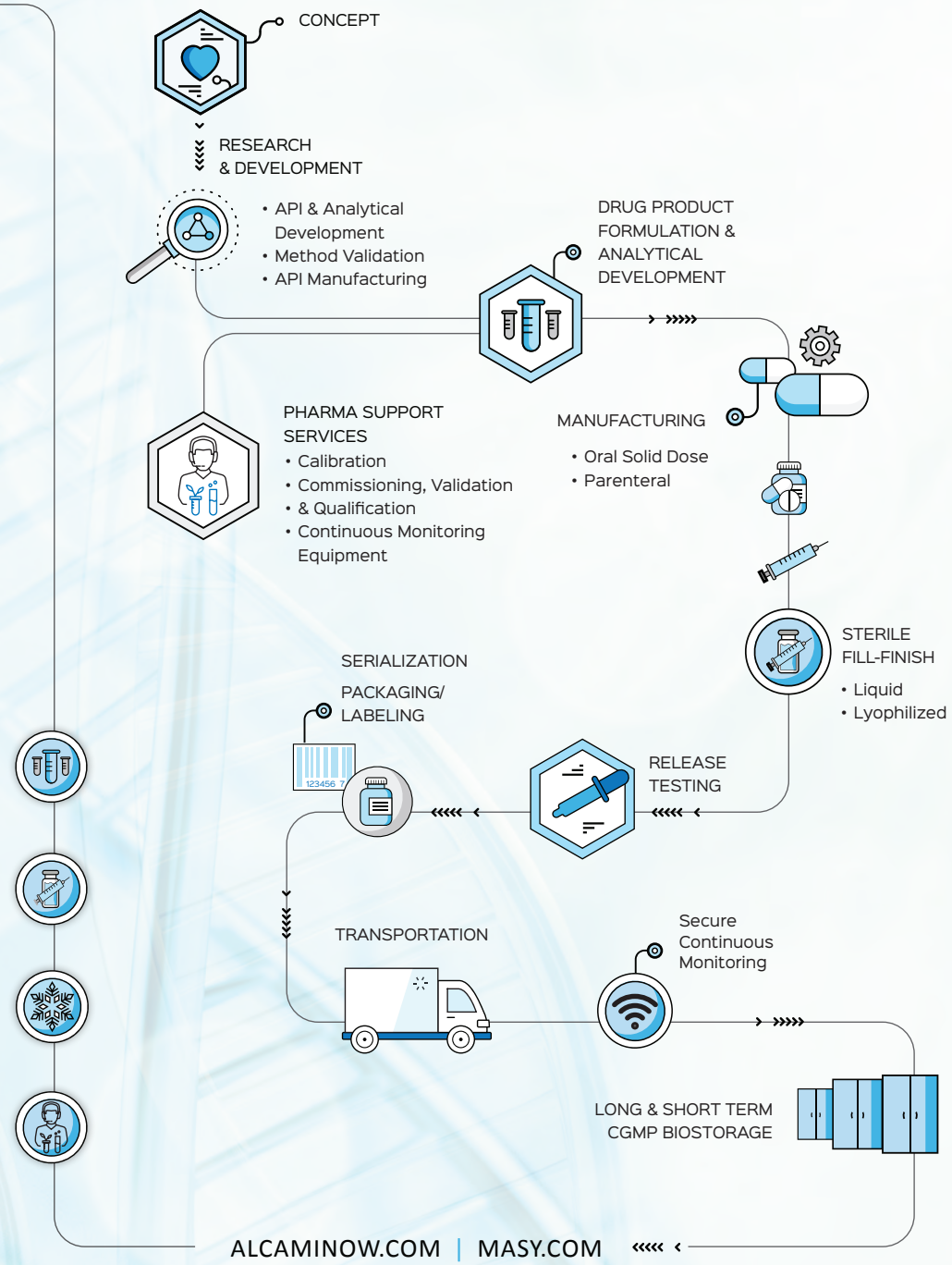

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Core Topic
Bioprocessing

Amgen's acquisition. Amgen and Horizon Therapeutics have reached an agreement with the Federal Trade Commission (FTC) that should allow the companies' planned acquisition to go ahead. The FTC moved to block the merger back in May after raising concerns that the deal would lead to a monopoly involving Horizon's Tepezza, used to treat thyroid eye disease, and Krystexxa, used to treat chronic refractory gout. The new agreement involves a consent order that would prohibit Amgen from bundling an Amgen product with Tepezza or Krystexxa. Several other conditions are also included in the consent order.

Henrietta Lacks settlement. Thermo Fisher Scientific has reached a settlement with the family of Henrietta Lacks regarding the HeLa cell line. Lacks died of cervical cancer in 1951, but cell samples were taken without her knowledge or consent, and used to create the immortal HeLa cell line. HeLa cells have since been used in countless medical advances. In 2021, the family filed a lawsuit against Thermo Fisher Scientific, accusing the company of "unjust enrichment" because it has continued to commercialize and profit from the cells. The terms of the settlement have not been disclosed, but both sides are said to be happy with the outcome. Lacks' estate originally demanded that the company pay back the full net profit obtained from commercializing the cells.

COVID-19 research update. Several countries have seen a rise in COVID-19 infections in recent months, with the WHO in August declaring the EG.5 strain a variant of interest – but also emphasizing that the public health risk is low. There is also plenty of research activity taking place. The Jackson Laboratory and Weill Cornell Medicine released research explaining how severe COVID-19 can affect gene expression in immune stem cells, triggering long-lasting alterations in immune response. On the drug development side, Novavax says its 2023-2024 season COVID-19 vaccine candidate induces an antibody response against EG.5. Regeneron has also announced an agreement with BARDA involving clinical development and manufacturing of an antibody to prevent COVID-19.

Leaked results at Roche. In August, Roche confessed there had been an "inadvertent disclosure" of an interim analysis of the company's phase III Skyscraper-01 trial involving anti-TIGIT immunotherapy tiragolumab. The leak appeared to show positive results (which rallied Roche shares), but Roche has stressed that the data is not mature. Data on the trial are due to be published early in 2024. Tiragolumab failed two trials in 2022 so a win now will be a huge boost for Roche.

IN OTHER NEWS

Sartorius and Repligen launch integrated system for upstream processing comprising Biostat STR bioreactor and XCell cell retention technology

Genentech fined $158,208 by the US Environmental Protection Agency for three hazardous waste violations concerning its South San Francisco facility

SK bioscience signs agreement with Republic of Serbia for strategic partnership in vaccine development and manufacturing

FDA places partial clinical hold on enrollment in Gilead's magrolimab trial for myeloid leukemia; reason for the hold has not been disclosed but patients in trial can continue treatment

Sandoz agrees development and commercialization deal with Samsung Bioepis regarding a biosimilar version of Janssen's Stelara (ustekinumab)

Llamas Versus Dengue

Why one company is focusing on camelid-derived antibodies to tackle dengue

Original Image: Wellcome Trust

Earlier this year, Neelika Malavige from the Drugs for Neglected Diseases initiative wrote about dengue – one of the most rapidly increasing mosquito borne infections in the world (1). There is a distinct lack of treatment options, but one company working on a new dengue therapeutic is ExeVir – the recent winner of a research grant from Flanders Innovation & Entrepreneurship (VLAIO). The grant will be used to identify highly potent heavy chain (VHH) antibody fragments against dengue that can be developed into VHH-based antibody constructs.

Dengue drug development is challenging in part due to the virus's four different serotypes. Fiona du Monceau, Chief Operating Officer at ExeVir, explains, "Generally, a first infection by one of the dengue serotypes causes either no or mild symptoms, followed by immunity against the infective serotype. However, due to neutralizing antibodies against this serotype that poorly recognize the other serotypes of dengue virus, a subsequent infection by a different serotype can cause severe, even life-threatening disease due to a phenomenon called antibody dependent enhancement (ADE) that leads to enhanced infections. Therefore, it is important to have a balanced response against all four serotypes."

Currently, no specific treatment is available and there are only two vaccines – both of which have limitations. According to du Monceau, "One can lead to ADE in sero-naive individuals upon subsequent infection by dengue viruses and the other is contraindicated in specific populations."

New approaches are needed – and not only for travelers and those currently living in endemic regions; global warming is allowing dengue to spread to new territories, including western Europe and the US. In fact, around half of the global population now lives in areas suitable for dengue transmission.

ExeVir's approach to a new dengue therapeutic makes use of VHH antibody fragments from camelids. Camelid-derived antibodies aren't unusual and are being researched for several areas, including rare diseases and oncology. ExeVir's VHH platform uses multi-specific antibodies with a potential half-life of six months, enabling prophylactic and therapeutic approaches to combat infectious diseases.

"These fragments are much smaller than human antibodies (12–15 kDa) with the potential to access unique and occluded epitopes that are often well conserved and more difficult to access by conventional monoclonal antibodies," says du Monceau. "They are modular in design giving flexibility to target epitopes on different sites, reducing viral escape, and, because of their smaller size, they have the potential for enhanced tissue penetration, with a lower dose and greater ease and cost-effective manufacturing."

In addition, there is increased manufacturing flexibility, with potential to use CHO or yeast platforms, such as Pichia. "The ability to produce VHH in Pichia will decrease manufacturing costs and hence increase affordability," says du Monceau.

ExeVir's innovative approach involves immunizing llamas to generate VHH

"There is increased manufacturing flexibility, with potential to use CHO or yeast platforms, such as Pichia."

libraries and so, depending on the infectious disease target, an optimal immunization agent must first be identified or designed. Furthermore, optimized immunization protocols are required to maximize the immune potential of the llama, as well as to identify VHH clones with the desired characteristics and efficacy.

And the work isn't finished there. "Humanization and sequence optimization of the llama-derived VHH is needed to minimize the risk of developing anti-drug antibody formation, based on the current scientific knowledge of which MHCII epitopes to avoid," says du Monceau. "But these manageable challenges do not outweigh the advantages that are inherent to the potential of VHHs – namely, their ability to reach highly conserved epitopes that are often hidden for conventional antibodies and the modular flexibility and ease of combining these VHHs into multi-specific antibody constructs to optimize potency and breadth."

ExeVir has also been investigating the viability of its technology for SARS-CoV-2 in individuals with an impaired immune system. du Monceau adds, "Our drug candidate XVR011 lost neutralization potency against Omicron BA.2 and subvariants, but it remains ready for phase II – subject to the appearance of susceptible SARS-CoV-2 variants. More importantly ExeVir has very promising 'second generation' molecules ready to advance into clinical development targeting both the S1 and the more conserved S2 region of the SARS-CoV-2 spike protein, and neutralizing all variants of concern to date."

Reference

1. *N Malavige, The Medicine Maker, "The Dangers of Dengue," (2023).*

Tooling Up for Biopharma's Digital Future

How digitalization will revolutionize the way we develop and optimize bioprocesses

Featuring Tiffany McLeod, Product Manager for Umetrics® Studio Partner Ecosystem, Sinyee Yau-Rose, Product Manager for Umetrics® Studio Insights Applications, and Chris McCready Principal Research Scientist – all from Sartorius

Would you say biopharma is on the brink of a digital revolution?

TM: We're all already living through an age of digital transformation, but in the biopharma industry, as a whole, we are still at the beginning. The hurdles of implementing anything new in biopharma will always be higher than in other fields because of the regulated nature of the industry. Today, however, many biopharma organizations are becoming increasingly interested in digital technologies because they are the key enablers of trends like single-use, process intensification, and continuous bioprocessing. Take continuous and intensified bioprocessing as an example. This pivot requires real-time monitoring and control, as well as the ability to measure and adapt. And to accomplish this, we need things like advanced sensors, online analytics, and real-time data acquisition to help us understand the health or state of the process, as well as models that can determine what to adjust to keep the process running smoothly.

CM: I believe that the industry is at the start of a revolution. With advancements in the modeling of cell culture and downstream processes, the industry is starting to realize the benefits of in-silico digital tools. The merging of mechanistic and digital streams give organizations the opportunity to evaluate the benefits of complex manufacturing systems, such as intensified or continuous processing, and reduce the burden of wet-lab experiments. The use of predictive models that can help inform advanced control decisions is a particular area of focus for the Advanced Data Analytics team at Sartorius.

SYR: There is definitely a great deal of innovation occurring in digital technology right now. One big enabling technology is cloud computing, which empowers organizations to build, test, and run scalable tools quickly. Clouds can help organizations, both large and small, to minimize IT support, while offering the ability to quickly upgrade computing resources or access advanced applications without needing to invest in extensive IT infrastructure.

How exactly can in silico tools accelerate process development in biopharma?

SYR: Reducing wet-lab experiments can make a big difference to the time (and costs) required for process development. Imagine trying to run 10,000 experiments in vitro – it's a huge and time-consuming challenge! But it can also be done with simulation tools. Scientists will already likely have many datasets from previous experiments that they can input into in silico tools to significantly increase the informational gains from each experiment.

CM: Intensified processes have the potential to reduce cost of goods and manufacturing footprints, but they also increase complexity. The hardware is more complex, requiring separation systems for perfusion, and there is much more to optimize. Given the complexity of the processes, wet-lab experiments are more expensive and time intensive. Enhancing process understanding generated from wet-lab experiments with simulations allows various system configurations to be rapidly evaluated. Many challenges can be first identified and resolved through simulation, saving wet lab experiments to verify simulation results or improve model resolution.

For example, we have developed a technique that can take fed-batch data (which is relatively simple to generate) and predict how a cell line will perform in intensified or continuous operation, where media exchange is introduced. Required perfusion rates and expectations of maximum stable cell densities can be estimated very quickly,

SARTORIUS

Understanding the Importance of Umetrics® Studio

Umetrics® Studio is a cloud-native data analytics and management ecosystem that enables model building and investigation, as well as data storage, visualization, and transformation for advanced insight generation. Sartorius acquired Umetrics® in 2017.

"Umetrics® Suite led the way in producing software tools to allow scientists and engineers to use design space and multivariate modelling methods to evaluate and summarize information in complex data," explains Chris McCready. "Today, Umetrics Studio is continuously evolving and will provide additional functionality and applications according to industry needs and in close collaboration with customers and partners."

Tiffany McLeod sees the Umetrics® Studio becoming the "App Store" of the bioprocessing world. "This is an enabling technology," she explains. "We have an impressive road map of applications that we have created at Sartorius, but we also want to enable customers and partners to add to the ecosystem by developing their own applications that they want to use internally."

Umetrics® was started by Svante Wold, a professor at Umea University in Sweden. Svante's father, Herman Wold, was an economist and is credited with developing the statistical method, partial least squares (PLS); Svante himself originated the term chemometrics. Svante and Umetrics® are considered pioneers in using digital tools to build understanding of complex manufacturing processes, particularly for batch type processes.

"Svante was involved in drafting FDA PAT guidance in 2004 that emphasized the use of science and risk-based approaches to manufacturing, including the use of multivariate tools [Guidance for Industry PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance, FDA, 2004]," says McCready. "Back in 2004, use of multivariate analytics for process monitoring and prediction of product quality was new to health science. Today, these techniques are accepted practice for detecting and diagnosing process faults. This is an early example of improving processes through digital tools – and just one example (of which there are many more!) that demonstrates Umetrics®' longstanding position as a leader in bringing digital tools to health science."

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without the need to run perfusion experiments. This information can then be used to estimate the potential benefit and trade-offs of continuous versus traditional fed-batch manufacturing system, without ever needing to run any media exchange experiments.

How else can tools from Sartorius help?

CM: Sartorius is building a foundation of bioprocess modelling capabilities, with a focus on streamlining process development and supporting manufacturing through monitoring and advanced control. Our mission is to have tools that are i) simple to calibrate (using data that is typically generating in process development or manufacturing) and ii) targeted to solve typical process development use cases.

TM: One tools I'd like to highlight is Cell Insights by Umetrics® Studio (see "Understanding the Importance of Umetrics® Studio"), which uses mechanistic models to generate bioreactor simulations. Cell Insights is bioreactor agnostic – which means that your bioreactor doesn't need to be a Sartorius product. With the simulations, users can, for example, select the best performing clone from a cell line or find out how changes in nutrients or the bioreactor environment will impact cell growth, metabolism, death, cytotoxicity, and so on. Notably, this information isn't just useful for early process development; it can also influence process optimization and scale up with simulations that show if your process is robust enough to perform well in a commercial manufacturing setting.

Another tool offered by Sartorius is BioPAT® Process Insights, which has been specifically designed to help Sartorius bioreactor users improve their scaling – and encourages the in silico exploration of new scaling approaches, using empirical models. Process Insights complements Cell Insights.

How does Sartorius account for useability when designing new digital tools?

SYR: Many analytical tools are perceived by bioprocess scientists to be too difficult to use (requiring a mathematical or data science background). And that has limited adoption – even though the amount of knowledge gained by using these tools can substantially transform process development without the need to change existing lab set ups.

At Sartorius, we wrap the advanced, computational engines of analytical tools in an intuitive user interface with guided workflows, so that non-data modelling experts can perform the analysis themselves and gain knowledge easily. As part of our UX design, we collaborated with different organizations. These are products designed by process scientists for process scientists!

TM: Traditionally, data scientists have played a crucial role in developing and applying computational models in bioprocessing. However, with new advancements in technology and, more organizations are starting to realize that you no longer have to be a data scientist or modeling expert to use these tools. That said, it's essential to note that while barriers have lowered, having a strong understanding of the underlying biologics and principals of bioprocessing remains valuable in interpreting results, making informed decisions, and troubleshooting issues. Companies taking a multidisciplinary and collaborative approach to digitalization projects are definitely ahead of the curve.

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Core Topic

Small Molecule Manufacture

Back of the net. Novartis' phase III NETTER-2 trial with Lutathera has met its primary endpoint. First line treatment with Lutathera, in combination with octreotide (a synthesized somatostatin), demonstrated a significant improvement in progression-free survival in patients with newly diagnosed somatostatin receptor-positive, grade 2 and 3, advanced gastroenteropancreatic neuroendocrine tumors versus octreotide alone. No new or unexpected safety findings were observed and the data runs complementary to the safety profile of Lutathera. Global Head of Oncology Development Jeff Legos said, "These positive results for Lutathera are quite remarkable and they represent the potential for radioligand therapy to make a meaningful impact."

Cort in the act. The UK Competition Appeal Tribunal unanimously upheld the Competition and Markets Authority's finding that pharmaceutical suppliers charged excessive prices for hydrocortisone tablets. Auden/Actavis UK was found to have increased prices by more than 10,000 percent (from 70 pence to £72) between 2008 and 2018, which was judged to have been an abuse of a dominant position. The companies, which now trade as Accord UK, have received fines of almost £130 million. CMA Executive Director Michael Grenfell said, "Following the actions of these companies, NHS spending on this essential medicine rose from around £0.5 million a year to over £80 million."

ARV versus HIV. The FDA has tentatively approved a New Drug Application from Viatris for its abacavir 60 mg/dolutegravir 5 mg/lamivudine 30 mg tablets for oral suspension for the treatment of HIV-1 infection in pediatric patients. The tentative approval shows the formulation meets all quality, safety, and efficacy regulations, and supports the company's sustainability goal to provide ARV therapy to two million children living with HIV/AIDS. The tentative approval facilitates regulatory authority submissions, production and distribution of the new child friendly formulation across 123 low- and middle-income countries as per the license agreement.

Smart alec. Roche's phase III study evaluating Alecensa (alectinib) compared with platinum-based chemotherapy has met its primary endpoint. Alecensa demonstrated a "statistically significant and clinically meaningful improvement" in disease-free survival in patients with ALK-positive non-small cell lung cancer. Alecensa is the first and only ALK inhibitor to demonstrate a reduction in the risk of disease recurrence or death in this indication. Results from the study will be presented at an upcoming medical meeting.

IN OTHER NEWS

Optibrium releases improved metabolism prediction capability in next generation drug discovery platform StarDrop 7.5

Sandoz completes acquisition of worldwide brand rights for antifungal agent Mycamine (micafungin sodium) from Astellas

EMA safety committee PRAC recommends new measures to avoid exposure of medicines containing topiramate during pregnancy

Exelixis and Insilico Medicine enter exclusive license agreement to develop and commercialize ISM3091, a potentially best-in-class small molecule inhibitor of USP1

Scientists in the Centre for Cancer Drug Discovery at the UK Institute of Cancer Research will work with researchers at Merck on a range of projects with the aim of discovering and developing new small-molecule cancer drugs

The Contaminated Childrens' Cough Syrup Scandal

Cough medicines made in India have led to the deaths of children

By Stephanie Sutton

Recent months have seen numerous reports in the media about contaminated cough medicines sourced from India. At least 78 children in Gambia experienced acute kidney injury (AKI) in 2022 because of contaminated cough and cold medicines; 66 of those children died. Most were under the age of two.

Health authorities in Gambia initially advised the public in September 2022 to suspend the use of all paracetamol and promethazine syrups. However, it was soon discovered that the medicines behind the injuries had all been imported from an Indian pharmaceutical company called Maiden Pharmaceuticals, leading the WHO to issue a global medical product alert. Four products from Maiden Pharmaceuticals were found to contain diethylene glycol (DEG) and ethylene glycol. DEG is toxic to humans and can cause death, but is sometimes used in place of more costly (and safer) diluents.

India's drug regulator performed its own tests and found no contamination, but there have been reports in the media that a bribe was potentially used to switch the samples before they were tested. Maiden Pharmaceuticals has now been shut down by Indian health authorities and Gambia's government is said to be exploring legal action.

The situation was also investigated by the Centers for Disease Control and Prevention. Their report, published in March 2023, explained how DEG-contaminated medicines are a particular threat to low income countries. "This likely poisoning event highlights the potential public health risks posed by the inadequate quality management of pharmaceutical exports," says the report. "Among reports of AKI associated with DEG-contaminated medical products, this is the first in which DEG-contaminated medications were imported into a country, rather than being domestically manufactured. Inadequate regulatory structures make the sale of medications from international markets an especially high-risk activity in low-resource settings."

The report goes on to explain that medications for export can potentially be subject to less rigorous regulatory standards than those for domestic use. In addition, low-resource countries may not have the resources to thoroughly monitor and test imported drugs.

The incident in Gambia was not a one off. In April of this year, a cough syrup in the Marshall Islands and Micronesia (GUAIFENESIN SYRUP TG SYRUP, manufactured by QP PHARMACHEM and marketed by TRILLIUM Pharma – both Indian companies) was found to contain unacceptable amounts of DEG and ethylene glycol.

And in July 2023, the WHO issued an alert for a cough syrup product in Cameroon called NATURCOLD. An analysis of the product samples identified unacceptable amounts of DEG – as much as 28.6 percent, when the acceptable limit for diethylene glycol is no more than 0.10 percent. An Indian company called Riemann Labs is believed to be linked to the medicines – and has since been told by Indian authorities to cease manufacturing activities.

The WHO has called on countries to be vigilant in preventing, detecting, and responding to incidents of substandard and falsified medicines after noting several incidents involving over-the-counter cough syrups for children. For manufacturers, the WHO urges companies to "only purchase pharmaceutical grade excipients from qualified and bona fide suppliers," and to conduct comprehensive testing.

In high income countries, such contamination of medicines is rare – and instances of mass poisoning and death are almost non-existent. Over-the-counter cough medicines should come with close-to-zero risk – especially if children are more likely to encounter them. They are well established and easy to manufacture – and there is plenty of literature from regulators and other sources that emphasizes the risks of DEG contamination.

How anyone can cut a single corner knowing their medicines may be used by those whose tiny bodies are more prone to poisoning from contamination is beyond me.

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Key Considerations When Partnering with a CDMO for Your Plasma-Derived Therapies

Experts from Emergent BioSolutions break down the qualities that make an ideal CDMO partner for plasma-based protein manufacturing

By Jeff Morier, Senior Scientist with the Manufacturing Sciences and Technology Group, and James O'Meara, Director of Manufacturing Operations Projects, both at Emergent BioSolutions

Plasma contains an array of beneficial constituents that, when purified and concentrated, can be administered as medicines to treat rare and complex diseases. The generation of complex plasma proteins is something that animals have developed over the course of evolution. For drug development, skill and expertise is required to isolate these proteins from the blood and purify them into commercially viable and effective concentrations – in a safe, controlled manner that does not damage or destroy their unique structure and properties.

Two particular challenges, however, make plasma protein purification more difficult than manufacturing processes for other types of therapeutics. First, the complex and variable nature of the plasma matrix requires careful consideration during the initial purification step. Plasma contains numerous proteins with very similar physicochemical properties, so a multi-modal approach is required to selectively purify the target molecule.

Second, plasma is derived from natural sources, so the validation of orthogonal virus reduction steps is crucial. Physical segregation of the plasma product throughout the production facility is also required as the product moves from one viral zone to the next to prevent cross contamination.

Ultimately, a well-developed and controlled process is key when working with plasma, but building a strong understanding of the design space and implementing robust process controls requires significant time, energy, and costs. Proteins are highly sensitive to environmental conditions, and even the most subtle of changes may have an amplified effect in a purification process. If a process is not well developed or well understood, these subtle changes can have a negative impact on the product yield and impurity profile.

It is important to employ well-trained, experienced manufacturing personnel who understand the specificity required to selectively purify the target plasma molecules from complex plasma matrixes.

It's also important to know how plasma proteins behave in chromatographic and tangential flow filtration (TFF) steps. Functions supporting manufacturing should also include experts with extensive knowledge of the complexities that surround plasma protein purification.

Seeking an external partner

Partnering with a CDMO experienced in this space can help overcome the challenges of working with plasma and

Key Questions When Selecting a CDMO

- **Personnel.** Does the CDMO have personnel with experience in the development, manufacture, and testing of plasma products?
- **Facility fit.** Does the facility have the equipment required to fit the process scale? Can the facility accommodate smaller early phase clinical batches and scale-up to commercial batch size? Does the CDMO have the necessary equipment, people, and systems to meet the intended manufacturing cadence?
- **Project management.** Does the CDMO have robust and dedicated project management systems that are closely integrated with the tech transfer, manufacturing, analytical, and quality teams?

An experienced CDMO team will help clients navigate the complexities of product development, formulation, assay development and transfer, process tech transfer, scale up, and commercialization. The right partner should also be well positioned to understand a client's process and product, interpret the facility needs, recommend alternative technologies when required, and demonstrate flexibility in navigating the path to commercial manufacture. A clear line of communication between client and CDMO is also integral to the success of the partnership.

Meet the Authors

Jeff Morier: *"During my career, I have been fortunate to work on numerous plasma projects. I have seen firsthand the direct link between the work I do and the impact it has on the patient. While each project has common elements, the variable nature of plasma-derived products means that there are always unique challenges to overcome."*

James O'Meara: *"My role includes building business relationships with potential clients who are seeking a partner to manufacture their product, from early phase clinical to commercialization. I'm very fortunate to have opportunities to collaborate with various clients and to experience the passion they have for their product – and the patient needs it will meet. Building a manufacturing strategy that delivers a quality product to that client is a very satisfying result."*

provide a more efficient path to clinical and commercial production. Companies with a lab or pilot scale process often lack the facilities or equipment to scale the process to a clinical or commercial level. For a company with products in early phase development, where product success has yet to be determined, investing heavily in capital expenditure to build a manufacturing space, purchase equipment, and recruit the appropriate team members can be risky.

When a client comes to a CDMO to make their product, they can leverage that CDMO's manufacturing capabilities and personnel expertise, with the expectation that they can deliver a quality product. CDMO's experienced in plasma protein purification, such as Emergent, already have the infrastructure, personnel, expertise, manufacturing equipment, and other resources in place to support development, tech transfer, scale up, and commercialization. Experienced CDMO's should also have supporting systems, such as expertise in materials management (procurement, shipping, testing, storage of plasma units, and so on), quality, and analytical services – and a robust project management system to ensure everything runs smoothly. A mature quality management system – coupled to a strong quality culture – is also a must.

Emergent's Center of Excellence for Plasma Proteins

Emergent has the manufacturing capabilities and capacity to support plasma-based products at any stage of development. For those with commercial products on the market, Emergent also offers contingency in terms of manufacturing continuity and to plan for fluctuations in market demand and future market growth.

Our facility in Winnipeg, Canada, is a Center of Excellence for plasma protein purification and has experience with manufacturing products that are approved or licenced in the United States and Canada. In fact, the plant has over three decades of experience in the production, purification, filling, and packaging of commercial plasma-derived products (from both human and animal sources).

We are also very proud of the excellent retention rate of our highly skilled and knowledgeable subject matter experts. The retention of expertise at the Winnipeg site is a testament to the strength of the working culture and a measure of the commitment and dedication to protecting and enhancing lives. This depth of high-quality expertise ensures that Emergent remains well-positioned to support clients in the successful development and execution of their plasma protein related processes.

By developing, manufacturing, and delivering our own well-established IgG products to the market, Emergent is uniquely positioned to support fellow biopharma innovators in successfully bringing plasma-derived therapies from development through tech transfer to commercialization.

Fabulously Interesting

Sitting Down With… Sharon L Rogers,
CEO of AmyriAD Therapeutics, CA, USA

What inspired you to pursue a career in your field?

Between undergraduate and graduate school, I was working at the Ohio State University in Columbus in a laboratory studying viral-chemical co-carcinogenesis related to asbestos. I was fascinated by how a virus and a chemical could work together to produce decrements in cell communication and replication. One usually thinks about viruses as engaging separately, not how they can interlink with a chemical and interfere with biological communication. Drug development is really all about cell communication and how you can modify it.

You're also an athlete. How did you become involved in Olympic figure skating?

I skated, but I'm not of the Olympic caliber at all. You have to be realistic about what you can do so I got into officiating, starting with little kids and moving through the ranks to the Olympic level. With those athletes, it's a different responsibility; they're a unique subset of athletes, but I just had a knack for it. I consider it an honor and I'm always trying to be mindful of how to pull the best out of them.

What research are you best known for?

A drug I developed (Aricept) has been the number one standard of care for Alzheimer's and dementia for over a quarter of a century. As a standalone achievement, it is a great accomplishment – but, if something has prevailed as a standard of care for 25 years, it reminds us that we have not done enough.

There's a movement toward disease modification in Alzheimer's, which came about because people believe they know what causes Alzheimer's – amyloid plaques and tau tangles. I believe these proteins are risk factors but the disease process is infinitely more complicated. For that reason, I continue to believe we need more agents to manage disease symptoms, with the goal of helping patients maintain independent function for as long as possible.

How did you become CEO of AmyriAD Therapeutics?

I was asked by the company's founders. AmyriAD has a portfolio of compounds all directed toward the treatment of Alzheimer's and, because I've had measurable success in a development field littered with failed studies, the founders had confidence their company would be in good hands with me.

What are you working on right now?

Our lead compound is a drug which we currently refer to as AD101. It is designed to improve neurotransmission in Alzheimer's patients, boosting both general cognition as well as independent global function. The drug has been studied and has completed phase I and II development, demonstrating a very good safety profile and significant improvement in both cognition and function. We are planning to move to large-scale phase III trials.

What other research developments have caught your eye?

All aspects of small molecule research are exciting in their own way, but I'm easily entertained on this topic! One standout moment was a project focusing on what was referred to as sepsis syndrome. We learned so much from that program, including how much we didn't know. People used to think sepsis syndrome was caused by a bacterial infection of the blood. We have since learned that what we called sepsis was really a massive inflammatory response we now call systemic inflammatory response syndrome (SIRS). SIRS can be produced by a viral, bacterial, or fungal infection – or with no infection at all other than significant inflammatory stress. It was fabulously interesting because we learned so much about the cascade of biochemical events that results in the syndrome. We also learned that you can stop it right in its tracks at one particular early step in the process – but, if you miss that step, the rest of the inflammatory cascade is likely going to happen. That information was just priceless.

Your appearance on our Power List taught us that you have an interest in politics and culture. How have those two things helped steer your career?

I'm always interested in how people use their voices in a way that is going to be of some benefit to humankind. The artist Banksy, for example, makes sociological statements that invite people to think about compassion in ways they might not have done before.

And then there is Janet Yellen. She is a tiny, white-haired lady who looks like everybody's grandma, and she wanted to emphasize how people's lives are affected by government decisions. She came under scrutiny for her choice of language in the White House, but she helped ensure that those downstream effects were mitigated. I'm attracted to people who do not give up on their core values.

What about your core values?

My personal values include looking at the bigger picture. We're all individuals, but we're part of a larger family, and everything I do in my work might impact employees, patients, and caregivers. Everything we do impacts something else, and you just never know how far that repercussion will spread. The decisions we make and the way we conduct ourselves can make us successful and profitable, but we should never forget who we are doing it for.

On days when your motivation runs low, how do you re-energize?

The most I can do is try to focus on the things that are going to be important and meaningful, while I block the rest of it out. Maybe that stems from my experience as an athlete; you learn how to tune out anything that's not going to help you keep putting one foot in front of the other.

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