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Saying Farewell to the Famous Horse Tweet

Why the FDA deleted its statement that people are not horses (or cows), referring to ivermectin use

Editorial



During the COVID-19 pandemic, some patients turned to ivermectin. In response, the FDA tweeted, “You are not a horse. You are not a cow. Seriously, y’all. Stop it.” The agency included a link to a page explaining why ivermectin should not be used to treat or prevent COVID-19. It was a brilliant move – a clear message on an important topic with a touch of humor – and it went viral.

Unfortunately for the FDA, their stance led to a lawsuit. Three doctors (Mary Talley Bowden, Paul Marik, and Robert Apter) claimed that the FDA overstepped its authority, interfered with their ability to prescribe, and harmed their reputations. Bowden lost admitting privileges at a hospital; Marik lost positions at a medical school and a hospital; and Apter was referred to physician regulatory boards for discipline – all because of their support for ivermectin to treat or prevent COVID-19.

The lawsuit was initially dismissed, but the decision was reversed in the Fifth Circuit Court of Appeals in September 2023, with Judge Don Willett stating: “FDA is not a physician. It has authority to inform, announce, and apprise – but not to endorse, denounce, or advise. The Doctors have plausibly alleged that FDA’s Posts fell on the wrong side of the line between telling about and telling to.” Thus, the lawsuit was free to proceed.

The FDA doesn’t have legal authority to limit off-label use of a drug approved for human use. Ivermectin is approved for prescription use in humans for conditions associated with parasitic worms, while veterinary ivermectin is readily available to purchase over the counter. So when some groups and influencers began endorsing the use of ivermectin against COVID-19 (despite numerous studies saying it had no effect), some people turned to ivermectin formulations meant for animals.

It is frustrating to see the FDA backed into a corner when the agency had public health in mind. Recently, the FDA reached an agreement in the lawsuit; the doctors would dismiss their claims but the FDA had to remove social media posts and consumer directives concerning ivermectin and COVID-19 – this includes pages that gave information on why ivermectin should not be used to treat COVID-19, as well as the famous horse tweet.

I’d love to hear your thoughts: stephanie.vine@texerepublishing.com.

Stephanie Vine
Group Editor



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Saying Farewell to the Famous Horse Tweet, by Stephanie Vine

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Innovation Winner

Lonza's Enprotect Capsule is the recipient of the 2023 Medicine Maker Innovation Award

Following a busy year for innovation in pharmaceutical manufacturing technologies – and many worthy nominees, we can now announce the grand winner of The Medicine Maker Innovation Awards...

Congratulations to Lonza and its Enprotect capsules!

The Innovation Awards is an annual showcase of new drug development and manufacturing technology available on the market. For 2023, nominations were, as usual, submitted via the website, with a shortlist being published in December 2023. Readers were then invited to vote for their favorite technology.

Lonza has a well-established history of developing and launching innovative oral solid dosage forms. Enprotect bi-layer capsules enable targeted release in the small intestine – exactly where (and when) it is needed. The HPMC inner layer provides the appropriate properties for forming a hard capsule in terms of manufacturing process and mechanical

properties, while the HPMC-AS outer layer ensures it opens or disintegrates in the small intestine rather than the stomach. The capsules are created using a manufacturing platform technology that can produce capsules with these two distinct layers, while maintaining standard dimensions. Notably, the manufacturing method does not require an enteric coating formulation, and there is no stress to sensitive APIs because they are filled directly into the capsule without further downstream processing.

Christian Seufert, President, Capsules & Health Ingredients, Lonza, said, "It is an honor for Lonza's Enprotect capsule to be recognized by The Medicine Maker and your readers. This innovative capsule solution for enteric drug delivery

results from a passionate and fruitful collaboration across our R&D teams that represents more than a scientific advancement; it is a testament to our dedication to meeting the evolving needs of our customers and their patients."

This year's runner up was TriLink's CleanCap M6 mRNA cap analog, designed to help researchers maximize the impact of mRNA therapeutics. According to the company, analog improves potency and increases mRNA yields with a capping efficiency of more than 95 percent.

Nominations for the 2024 Innovation Awards will open soon. Sign up for our newsletter via our website to be the first to find out when the nomination form is live.

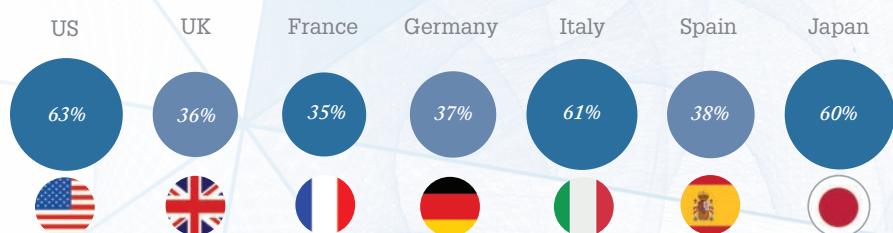


INFOGRAPHIC

Generic or Branded?

Should patients be given an option to choose whether they are prescribed a branded or generic drug? GlobalData asked this question to 295 healthcare industry professionals. Here are the results.

Yes



Source: GlobalData, "Generic Drugs – Physician Perspective – Thematic Intelligence," (2024).



REGULATION

- IN - BRIEF

A look at some of the biggest regulatory headlines in the industry

- The EMA has published recommendations to strengthen supply chains in Europe and prevent shortages of critical medicines. EMA's Medicines Shortages Steering Group will now work to develop regulatory and governmental policies. Potential actions include recommending that marketing authorization holders increase production capacity, implement monitoring forecasts of supply and demand, diversify their supply chains, and put in place shortage prevention plans.
- Continuing to address quality and performance issues with plastic syringes made in China, the FDA has issued a warning letter to Cardinal Health – after the company was found to be importing and distributing products and components made by Chinese companies, who have previously received warning letters for devices that do not meet quality requirements.
- In another win for Biden's drug price negotiation program in the US, a federal judge in New Jersey has rejected legal challenges from J&J and Bristol Myers Squibb. The big pharma companies had argued that the drug price negotiation program was unconstitutional, but the judge ruled that participation in the negotiation process, and in Medicare and Medicaid, is voluntary.
- Report in the UK from Nuffield Trust has examined the impact of Brexit on drug shortages. Shortages have increased globally, but the report adds that Brexit has worsened the situation in the UK by removing the country from EU supply chains. Life science and medicine regulation, including new drug approvals, are also seen to be lagging behind those in the EU. Between December 2022 and December 2023, four drugs approved by the EC were approved faster in the UK, but 56 were approved later. As of March 2024, 8 drugs approved by the EC had not been approved in the UK at all.

A Star Is Warned

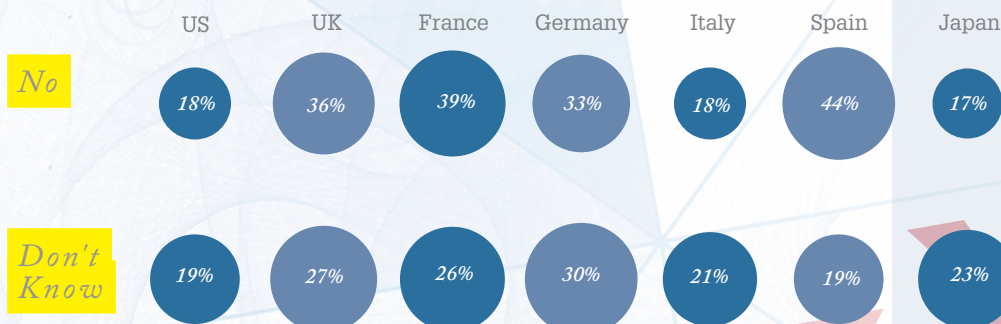
Lady Gaga under fire for a migraine treatment ad

Superstar Lady Gaga's latest promotion of Pfizer's migraine treatment Nurtec ODT (rimegepant) in the US has come under criticism after it was deemed to have violated EU rules on direct marketing. Although the singer turned actress added a disclaimer stating that the posts are "intended for U.S. audiences only," Gaga's Instagram post was not restricted to a US audience, and thereby in conflict with both the EU Digital Services Act and Digital Markets Act. The latter states that infringements could result in fines "of up to 10% of the company's total worldwide annual turnover, or up to 20% in the event of repeated infringements."

Fans of Lady Gaga have also criticized her for "selling out" to the pharmaceuticals giant.

The partnership with Pfizer has invited controversy regarding the role of celebrities in promoting pharmaceutical products. The conflict lies between raising awareness and destigmatizing conditions, and the influence of for-profit corporations on public health messaging.

Credit: Lee Chu, CC BY-SA 2.0, via Wikimedia Commons



ADCs Versus Solid Tumors

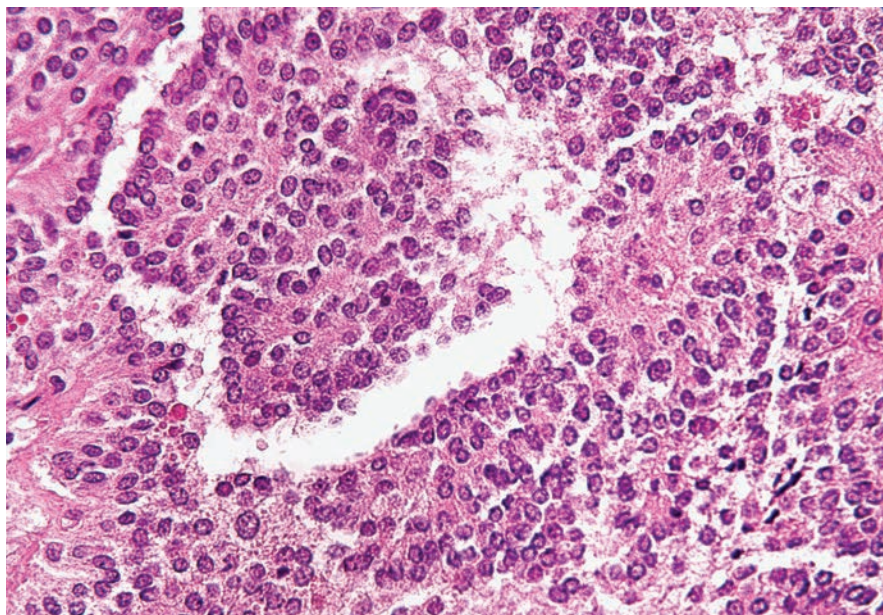
Drug developers place their bets on the ROR-1 antigen in the battle against solid tumors

Ipsen has secured development rights for ADC STRO-003 from Sutro Biopharma in a deal that could be worth around \$900 million. The drug candidate uses Sutro's proprietary XpressCF+ platform and Beta-Glu site-specific conjugation linker technology – and targets tumor antigen ROR1, which has also caught the interest of big pharma companies, such as Boehringer Ingelheim.

Mary Jane Hinrichs, SVP, Head of Early Development at Ipsen, says, “ROR-1 antigens are present on numerous solid tumors and hematological malignancies, but there is currently no approved ADC targeting ROR-1. ROR-1 can also offer potential advantages in terms of safety profile, with low normal tissue expression minimizing potential toxicities for patients – but this will be better understood during clinical evaluation. Early data has shown strong potential for STRO-003 as a monotherapy with

robust efficacy in solid tumor models and promising clinical safety profile.”

Ipsen will now be focusing on achieving proof of concept in solid tumors. Although this will be the company's first ADC, Hinrichs says they have been watching the ADC space closely for some time – learning from the progress and challenges being seen across the industry. A recent evaluation of the ADC landscape showed that, of approximately 260 ADCs in development, only 11 are approved – reinforcing how challenging it is to strike the perfect balance to optimize all three components and create a stable ADC that can reach and act on the target cancer.



“Where the community has faced challenges is how to effectively maximize all three components of an ADC, without compromising one for the benefit of another. A promising agent may not offer optimal stability when paired with an antibody, for example,” says Hinrichs. “It's important to remember that some challenges should also be celebrated by recognizing their scientific value – the questions they have answered and the direction they have given to shape future progress.”

Ipsen is excited about the potential for STRO-003 because Sutro technology maintains stability of the payload and results in a highly stable molecule. Moreover, the novel payload, exatecan, has shown significant potential in solid tumors.

Count Bac-ula

Scientists discover vampirical traits of bacteria

Washington State University researchers have found that certain bacteria can sense and navigate towards blood serum – specifically the amino acid serine – which they consume as nourishment in a phenomenon labeled as “bacterial vampirism.” Published in

eLife (DOI: 10.7554/eLife.93178.2), the study investigates the root causes and potential treatments of bloodstream infections. At least three types of bacteria known to be leading causes of death in patients with IBD, *Salmonella enterica*, *Escherichia coli*, and *Citrobacter koseri*, are attracted to human serum, with intestinal bleeding as a symptom being one possible ingress

into the bloodstream. Corresponding author Arden Baylink said, “We learned some of the bacteria that most commonly cause bloodstream infections actually sense a chemical in human blood and swim toward it.” Further studies aim to develop drugs that block the ability to “swim” toward blood serum for the treatment of patients at high risk of bloodstream infections.

Time is many things.

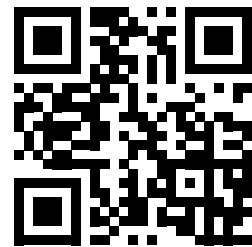
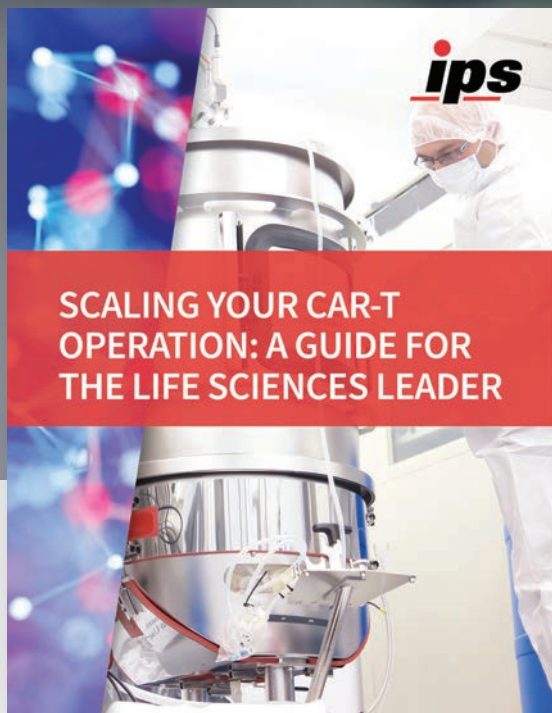
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The Quest for the Golden Batch

Knowledge (or data) is power when it comes to batch-quality prediction and obtaining the coveted perfect profile

By Eoghan Moloney, Associate Director of Projects, Life Sciences Manufacturing at Cognizant

Batch quality is a critical metric – not only because safeguarding patient health is paramount, but also because poor quality affects bottom lines and profitability. The cost of a single batch deviation can be anywhere from \$20,000 to \$1 million per batch, depending on the nature of the product.

Until recently, the only way to analyze historical and time-series data to explore and understand batch deviations was for subject matter experts (SMEs) to spend considerable time manually reviewing spreadsheets. The SMEs would extract production data by hand, populate a spreadsheet, and create graphs. These graphs would then be used to create process parameter profiles to serve as guides for reducing process variability and increasing yield for all future batch development. In other words, creating the “golden batch profile.”

However, this manual approach is increasingly unfit for purpose and unable to help SMEs accurately identify relationships between data points. The current method presents two key issues:

Golden batch profiles require many hours to be spent manually sifting through years of data or delayed lab results, which makes it hard to optimize process inputs to manage batch yield.

Out-of-tolerance events will still occur, regardless of applying diligence in controlling critical process parameters

(CPPs) of a recipe, as measured by a group of critical quality attributes (CQAs).

The number of variables and the cause-and-effect relationships connecting these two aspects are more complex than originally assumed. Pharmaceutical manufacturers already have the data they need to optimize their operations. What is needed is a method to analyze it all efficiently.

With this in mind, it is no surprise that a growing number of pharma companies are transitioning to advanced analytics to simplify the process of identifying their golden batch profile. New live connectivity solutions can eliminate the need for manual input into spreadsheets and facilitate data cleansing, contextualization, aggregation, and near-real-time process data analysis. A live connection between all relevant sources of data allows SMEs to minimize the time they spend collating data and aligning time stamps by hand.

Advanced analytics platforms for process manufacturing can also be integrated across every area of an organization’s operations, running in a browser with live connections to all process historians to quickly extract data to be analyzed.

To understand where advanced analytics can have real-world benefits, it is worth considering a specific use case,

such as examining a production process with six CPPs connected to a single unit procedure. Historical data from ideal batches with acceptable specifications on all CQAs can be easily used to graph the six variables from all the previous unit procedures. Curves representing performance from historical CPPs can then be superimposed on top of each

In My View

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



“It is no surprise that a growing number of pharma companies are transitioning to advanced analytics to simplify the process of identifying their golden batch profile.”

other using identical scales to uncover new insights that can improve future performance.

Taking this approach, it is immediately clear if the curves form a tight group, or if they are spread across the graph, showing variation in values and times. Advanced analytics can easily aggregate these curves without the need for complex formulas or macros to determine the ideal profile for each CPP. Engineers can replicate this procedure to update the reference profile and boundary for each variable. The result is a better understanding of where there are opportunities to optimize processes.

For example, an upstream biopharma manufacturer harnessed the advanced analytics platform, Seeq, to study the cell culture process. With this technology, the manufacturer could create a model for product concentration based on historical batches to find the CPPs that produce the ideal batch. The company can deploy the model on future batches with golden batch profiles for all of its CPPs to track deviations more effectively and prevent them from recurring.

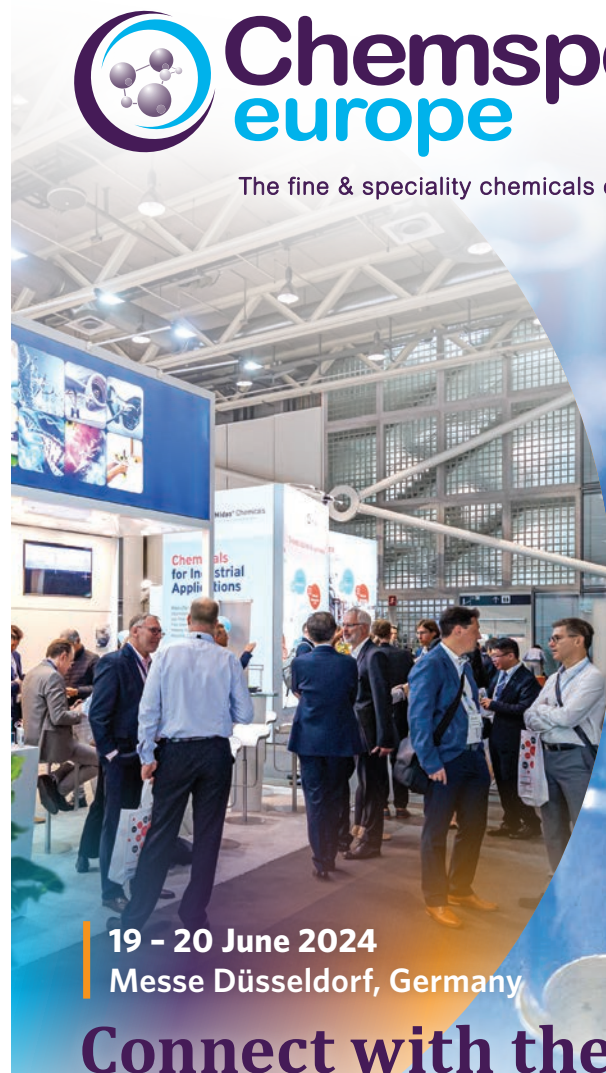
In another example, a manufacturer used the same technology to rapidly identify and analyze root cause analysis of abnormal batches. The team reduced the number of out-of-specification batches by adjusting process parameters during the batch, reducing wasted energy and materials – and saving millions of dollars.

Bristol-Myers Squibb uses advanced analytics alongside other technologies to capture information needed to test the uniformity of its column-packing processes. The company deploys Seeq to rapidly identify data of interest for conductivity testing to calculate asymmetry, summarize data, and plot curves for verification by SMEs (1). By calculating a CPP and distributing it across the entire enterprise, all team members can operationalize their analytics, providing rapid and reliable insight as to when a column was packed correctly. This prevents product losses and quality issues – and even complete batch loss.

Whatever the use case, it is my view that advanced analytics represent the future of batch quality optimization for the pharmaceutical industry. Harnessing the latest developments in digital transformation, machine learning and Industry 4.0, advanced analytics can give a company's engineers the insight they need to make better, evidence-based decisions. As a result, they will be empowered to go even further in optimizing the performance of day-to-day operations.

Reference

1. *ARC Insights, "Bristol-Myers Squibb improves chromatography and batch comparisons using data and analytics" (2018).*


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4. PHARMA

*Welcome to the
age of advanced
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in pharma*

Drug development is changing. Therapeutic modalities are expanding and one-dose cures are now a possibility for some indications. The pharma industry works at the cutting edge of biological sciences, and the technologies used for manufacturing should be as advanced as the therapies themselves. To create products faster, cost effectively, and more efficiently, companies should be leveraging the edge that technology can give: from AI to automation and digital enablement.

In this feature, experts in the cell and gene space discuss how Industry 4.0 is affecting the future of these therapies. But it's not all about cell and gene; all areas of pharma are advancing beyond expectations for the benefit of patients.

By Rob Coker



Introducing the Experts

Jason Foster, CEO of Ori Biotech, believes that automation and digitization are crucial for the future of manufacturing, particularly for cell and gene. Foster is working towards bringing these Industry 4.0 solutions to advanced therapies.

Matthew Lakelin, Head of Consultancy Services & Co-Founder at TrakCel, understands that the number of partners needed for the development and manufacture of a cell therapy can create a logistical nightmare, in which paperwork can seem to take over. The company develops digital solutions for clinical trials and commercial therapies.

Josh Ludwig, Global Director of ScaleReady, recognizes the potential that automation could have for cell therapy scale up. Using the company's suite of tools, Ludwig has helped partners develop new approaches to achieve reversible scalability, building an efficient process that gets advanced therapies to patients faster.

Barbara Ressler, VP, Manufacturing Process Sciences of RoslinCT, is responsible for managing the analytical development, process development, and manufacturing sciences and technology teams. The goal is to create robust, GMP-compliant processes and assays for the company's partners and to facilitate transfer to manufacturing and QC.



Cell and Gene 4.0

May the fourth industrial revolution be with you...

Unstoppable innovation in numerous fields has driven us to where we are today: Industry 4.0.

Arguably, the pharmaceutical industry has the opportunity to surpass the efforts of all other sectors with the wonder products being developed in the advanced therapy space; curing illness with a single dose surely represents the imaginable pinnacle of medicine. But the technologies required to manufacture these products – swiftly, accurately, cost effectively, at scale, and under extremely demanding regulatory requirements – must be as advanced as the therapies themselves or stakeholders risk being left behind.

The cell and gene therapy space may not quite be the final frontier, but it is fascinating to learn that, as we find ourselves a quarter of the way through the 21st century, innovators and enablers are still going boldly beyond expectations so that one day, just maybe, we can all live long and prosper.

Here, we gather four experts to help make sense of the varying definitions of Industry 4.0 – and what the fourth industrial

revolution has in store for the current and future of cell and gene therapy manufacturing.

How do you define Industry 4.0?

Barbara Ressler: Industry 4.0 is the digitalization of manufacturing; real time manufacturing readouts, real time analysis, and automatic controls. For cell and gene therapies, these technologies can help ensure the product is consistently made the same way every time – regardless of donor variation.

Matthew Lakelin: When I think of Industry 4.0, I think of connectivity – and using analytics and data to improve processing. Traditionally, much of the information in drug development has been siloed. Being able to analyze data across the whole value chain is really important. When it comes to Industry 4.0 tech, we also need to think about how we can interact with technology. Right now, the human–technology interface is still in its infancy, but collaboration can push it forward. I don't think any individual company or service provider can do it alone.

Jason Foster: Industry 4.0 is particularly important for cell and gene therapies. These medicines are inherently variable and don't lend themselves to GMP as we understand it for more traditional modalities. Having the ability to perform adaptive control, and to build and modify a process around the needs of particular patient cells to create the same outcome, is where we'd all ideally like to be. To achieve this, new sensor technology, real time analytics (and the ability to react to those analytics), IoT devices, and automation will all be a huge help. Right now, we're somewhere in between Industry 2.0 and 3.0. A lot of paper-based processes are still used for cell and gene therapies, including paper batch records and paper lab notebooks that use disconnected devices or lab-scale tools that aren't digitized at all.

Josh Ludwig: I agree with what the others have said. However, I would also add that, before we can truly take advantage of the Industry 4.0 technologies being developed today, we first need to ask, as an industry, how we can become really good at manufacturing cells consistently. Once we really understand the process, we can optimize it even further using Industry 4.0 technology.

What progress is being made?

JF: One of our companies has instituted batch release by exception, through a continuous validation process that uses digital technology. That's Industry 4.0 stuff right there.

Batch release is a huge challenge for personalized medicine. With traditional small molecules, a batch can be millions of tablets. For a personalized medicine, each batch is one therapy. No matter how good we get at the rest of the manufacturing process, batch release will always become a bottleneck at scale; you can't treat 10,000 patients if it takes a day to release two doses.

BR: Release by exception is our dream and we are trying to implement that too. Every cell and gene product is unique and each partner brings their own unique process, which makes electronic batch records (EBR) difficult. I am very much in favor of some version of standardization to make progress. I also want to see more digital control in the manufacturing process, but we're still quite far from this being a reality.

ML: Pharma companies used to be reluctant to have GxP software on cloud-based systems, instead wanting to keep their data on premises. This may work for some modalities, but cell and gene therapies have disparate supply chains with many different stakeholders. Here, cloud-based systems make a huge difference

by harmonizing supply chains. Something as simple as sharing information concerning manufacturing capacity with different sets of clinical centers, so that they know when they can schedule starting material collection can be difficult with a siloed approach. The cloud has made data sharing much easier.

I also believe that these types of technologies are encouraging more companies to add cell and gene therapies to their pipelines because developers can see how manufacturing and supply chains can be effectively managed. Now, we need to focus on scale-up and scale-out so that more patients can be reached.

JF: Scale up is a key topic. We're starting to get critical mass with numbers of products, but large numbers of patients remain untreated. It's time to consider what lessons have been learned and to ask: how do we refashion the infrastructure? Implementation of Industry 4.0 needs to be done carefully. Yes, there are new technologies and standards being developed that help us to talk to each other and help share data, structures, and frameworks, but all of this needs to be put together in a way that makes sense. We must avoid the "cobbled together" approach. Much has been learned over the last six years or so, but it's time for us to make sure we're coming together and creating real momentum towards Industry 4.0.

How do we accelerate industry-wide adoption?

ML: When you're thinking about uptake and new solutions, the mantra is "the process is the product." If you have an approved biologics license application or approved marketing authorization application, there aren't many incentives to change your process. In fact, making substantial amends to a marketing authorization will probably keep quite a few people up late at night with worry about

"We need to strip away all the needless complexity and just get back to what works, which is delivering oxygen and nutrients to cells, on demand."

the consequences! The pharma industry is naturally conservative, so adopting anything new is challenging. This is the mindset we need to somehow overcome.

BR: Our partner base tends to bring in fairly advanced academic processes; they don't want to change anything because of their preclinical efficacy data or their phase I data. They are trying to avoid what I (lovingly) call "death by comparability." Adopting new technologies scares new discovery companies, so reluctance is a real problem. We need a more unified comparability set of standards – a clear path forward so that companies really understand how to demonstrate comparability and easily validate a process change where the product is just as potent. This leads me onto the potency assay, which is, I think, the industry's Achilles heel in many ways. We need robust – and preferably standard – potency assays.

JF: I would say that we need investor buy-in. Adoption of advanced manufacturing technology and/or digital technologies needs to happen early in the process before reaching the clinic. However, investors have traditionally pushed new therapeutic companies to get into the clinic as fast as possible – leaving little time to focus on digitization and optimization. Incentives in the early development phase need to be aligned. Investors should give their portfolio companies and research partners time to develop a robust process that is repeatable, reliable, and comparable, which is the best foundation for clinical success.

What role must technology companies play in helping the cell and gene therapy sector move to Industry 4.0?

JL: I'm confident that developers and enabling technology companies are working to create common sense manufacturing platform principles. It should help us move faster, and then we can incorporate some of the really cool new stuff that will enable us to analyze blood on the front end and put them into different manufacturing workflows depending on specific cancer mutations. That's the next drive forward, but we can't get there unless we simplify. We need to strip away all the needless complexity and just get back to what works, which is delivering oxygen and nutrients to cells, on demand.

JF: The old model of getting great clinical data and getting bought out in phase II no longer applies to advanced therapies. Companies need to prove that their product will be commercially successful, which means thinking about widespread patient access and affordability. We know that Industry 4.0 has benefits, but it's not easy for drug developers to focus on this area. Drug developers are not software coders nor automation/robotics experts.

Technology developers need to do the heavy lifting here and convince scientists in the academic lab to use their technologies to help them achieve scale. We need both flexibility and scalability – not one or the other. Enabling technology companies need to make sure that can happen for the industry.

In cell and gene, we tend to think we're special – that it's okay for us to charge up to \$4 million for a product. But we are not just competing with other cell and gene products, we are competing with ADCs, small molecules, and biologics, which are also seeing amazing advances. We need to conform to the same rules as every pharmaceutical product – and products need to be affordable and accessible.

How do you think Industry 4.0 will continue to improve manufacturing?

ML: Although using generative AI in a highly regulated environment may still be a way off, predictive AI is certainly beginning to gather speed in terms of possible use cases. For manufacturing, this could result in more accurate forecasting of drug product demand or more responsive and intelligent scheduling of manufacturing slots, particularly where external factors make these changeable. Using AI in tandem with patient data, supply chain data, and other information could also make it easier to predict which shipping routes or channels hold the lowest chance of delay, which patients might require rearrangement of their treatment date, or make it easier to backfill canceled slots. This has the potential to leverage major efficiency increases. There may even be more that can be done to help mitigate for the varying quality of starting materials within cell and gene to make the production of consistent therapy products less of a challenge.

JL: Venture money, along with pharma deals, will continue to be hard to come by in cell and gene unless we as an industry make meaningful strides to reduce the cost to produce these therapies. Overly complicated manufacturing, which leads to way-too-costly drugs, will continue to be the roadblock in getting more therapies to market. Industry 4.0 could have a major impact on driving down production costs, but only after we first become ruthless in our effort to simplify the manufacturing protocols across the board.

BR: We are already seeing the benefits of Industry 4.0 in CGT manufacturing by the implementation of electronic batch records, release by exception, and improved sensory process controls. Even so, these digital solutions are challenging to implement for cell therapy manufacturing in its current state, particularly for autologous therapies. Advanced analytics will continue to improve

“Our industry cannot perpetuate the current rate, where incredible science and therapies showing great clinical benefit are failing due to the inability of biotech organizations to keep the lights on.”

process control and product quality; robotics and automation have the potential to reduce manufacturing errors and labor costs; and advanced engineering, such as nanoparticles, will improve payload delivery to cells for more robust gene editing.

Industry 4.0 could help turn science fiction into reality. Please present a sci-fi comparison or prediction of what you think the next five years will look like...

JL: Imagine a scenario reminiscent of “The Matrix,” where customized therapies are readily available, tailored to individual patients’ needs. Imagine smart factories employing augmented reality with real-time monitoring and intervention, ensuring the highest product quality and efficiency within manufacturing every single time.

But we must be patient. What we risk by injecting this sci-fi future too soon is baking in overly complex and incredibly expensive processes, and ultimately causing the downfall of otherwise excellent science as viable companies burn cash on complexities rather than focusing on the art of simplification. Our industry cannot perpetuate the current rate, where incredible science and therapies showing great clinical benefit are failing due to the inability of biotech organizations to keep the lights on. The groups focusing on simplification will reap the rewards in the form of added efficiencies (and therefore profit) that Industry 4.0 will bring.

BR: Five years is a short time horizon for the next chapter of cell and gene therapies. The industry is trending toward allogeneic

cell therapies, with a goal of highly effective, off-the-shelf, more affordable therapeutics. Perhaps in the next five years a successful allogeneic trial will herald the dawn of the allogeneic era, much like Kymriah brought autologous CAR-T to marketing reality.

Allogeneic cell therapies are even more dependent than autologous cell therapies on the quality of the starting material, and the cell therapy space still uses primary human tissues as a source. AI may be used to select the optimum donor material for allogeneic therapies that would far exceed our current abilities to screen donors. This is a less frightening and ethically fraught version of the genetic manipulation and selection in movies such as “Gattaca.”

JF: People have nightmares of robots taking control – think of “2001: A Space Odyssey” or “The Terminator” – but the near-term technological advances are going to look a lot more like “Star Trek,” where advanced technologies are omnipresent but frequently behind the scenes, augmenting existing capabilities, automating manual processes, and completing calculations and making inferences that humans cannot.

In the coming years, we’ll see an ease in demand for highly educated staff to do manual process monitoring. We’ll see improved IoT interconnectivity and data analytics that help us monitor and intervene to improve the quality and safety of individual batches to help us draw deeper insights that will drive the industry toward standardization.

ML: An old analogy but one that will be familiar to many is the use of the “Star Trek” medical tricorder. It was initially a scanning and analytical diagnosis device, but the intention is what always struck me; in the future, we would have sufficient knowledge and analytical power to offer each patient a treatment specifically tailored to them. This is what we are now seeing in advanced therapies; a field of medicine that can manipulate cells on a patient-by-patient basis to offer hope of a treatment not previously possible. Typically, CAR-T treatments are a therapy of last resort administered once standard of care chemotherapy has failed.

“Star Trek” storylines were always underwritten by the drive to push the boundaries of scientific discovery. These crews were constantly solving problems that had previously been impossible and making them faster or better than expected. We are privileged to see this in the cell and gene industry every day. Whether a new methodology or a new indication, those frontiers are continually being challenged. Until the point where the equally well-known “Star Trek” replicators and teleporters become a reality, we should all continue to strive to ensure that cell and gene therapies can reach as many patients as possible.

What the Future Holds

We asked a group of experts to make a prediction for the far-flung future of the industry that may seem like science fiction but could one day be a reality... and digital technology is a key theme.



James Riddle, SVP Global Review Services, Advvarra

The potential promise of gene therapy to proactively correct potential genetic predispositions is the stuff of Star Trek! For instance, we now know that people with certain genetic traits are more susceptible to breast cancer. Imagine a time in the not-too-distant future where gene editing has advanced to the stage where someone in their early 20s can have a gene editing therapy to “correct” the genetic trait and thus significantly reduce their risk of developing breast cancer 30 or 40 years later! That type of technology is not that far off. It’s an exciting time, such that we can start to remove the word “fiction” in today’s science fiction shows, books, and movies.



Joel Morse, co-founder and CEO, Curavit Clinical Research

I envision a world where every person will have their own “personal health record” that follows them and their health everywhere they go. This record will contain complete data from their interaction with medical infrastructure, device data, nutrition, economic, and mental health data, which will be seamlessly updated and the individual will always have access to it.



Jane Osbourn, CSO, Alchemab Therapeutics

Every individual will have their health status continually monitored using digital technologies and their data stored in a personal cloud which will alert them and their healthcare professional when action needs to be taken. The data will be integrated across large cohorts of individuals to provide increasingly accurate insights into continued wellness. Disease prevention will be valued as much as treatment.



Raquel Izumi, Chief Operations Officer, President, and Founder, Vincerx Pharma

I think at some point we are all going to have our genomes sequenced. Given the advances in AI technology, there will be predictive algorithms that can say which diseases we are predisposed to. With that information will come recommendations, such as lifestyle changes and/or prophylaxis medication, to help reduce the risk of developing those diseases.



Edward Haeggström, CEO, Nanoform

I have publicly stated that my company will try to double the number of medicines that reach the market each year, with the same R&D expenditure. I was inspired by the tricorder in Star Trek and I like the idea of going where other people have not gone before.

AI: Hype or High Performance?

Generative chemistry and other exciting applications of artificial intelligence in small molecule drug discovery

By Michael Parker, Principal Scientist at Optibrium

Depending on who you speak to, AI will either save or destroy the world. Rhetoric around AI making jobs obsolete remains, but perceptions are also now shifting towards embracing the usefulness of AI. Exciting tools, such as DeepMind's AlphaFold protein structure prediction software, regularly make headline news, and there is a growing realization of the potential time, money, and resource savings that could be achieved by adopting AI in drug discovery. Reducing the number of required experiments, screening larger databases than ever before, streamlining workflows, idea generation, and synthesis predictions are just a few examples of the benefits of AI.

When it comes to synthesis prediction, AI has made great strides due to the sheer volume of published literature now available for it to trawl through. However, the intricacies of identifying a feasible synthetic route can be tricky for current AIs to predict. Reagents, reaction parameters, and multi-step syntheses lead to a complex matrix of factors to consider. In recent years, however, new retrosynthesis software has developed to allow for more accurate synthesis planning,

train than other model types – and they work with bigger data sets. Harnessing transformers will enable drug discovery scientists to explore more chemical space. Taking a forward-looking perspective, it seems clear to me that these types of models will become more prevalent, supporting drug discovery scientists to ideate a wider variety of chemical structures, with better confidence in their synthetic accessibility.

Whilst considering compound ideas, scientists also need to identify those with sensible property profiles that fit their specific project. Multi-parameter optimization across complex absorption, distribution, metabolism, excretion, and toxicity properties can be difficult, with most AI platforms struggling to provide suggestions for previously unseen compounds or across the necessary numbers of endpoints. This area has huge potential. Gaining pharmacokinetic data experimentally can be very time-consuming and resource intensive. Often, this experimental data is “noisy,” with errors and outliers, and “sparse,” because of the difficulty in collecting data for all the areas a scientist may be interested in for every compound.

Cutting-edge deep learning algorithms can be used to impute missing data alongside their uncertainties, to highlight compounds with the highest chance of success and best potential property profiles. This approach has huge potential for streamlining innovation, reducing the number of necessary experiments, and guiding experiment prioritization to increase the efficiency of the drug discovery pipeline.

Sparkling ideas through generative chemistry

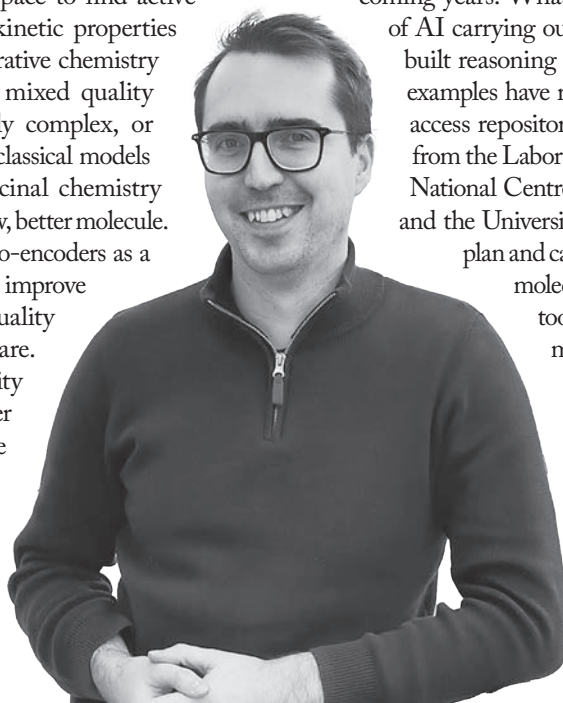
Exploring the vastness of chemical space to find active compounds with suitable pharmacokinetic properties is challenging. Early attempts at generative chemistry software tended to provide poor or mixed quality suggestions of unstable, synthetically complex, or inaccessible molecules. These previous classical models focused on iteratively applying medicinal chemistry transformations to eventually get to a new, better molecule.

The dawn of AI in this field saw auto-encoders as a popular machine learning approach to improve the span of chemical space and the quality of suggestions provided by the software. However, more recently the community has started turning towards transformer models. These AI models are the foundations of large language models (LLMs), such as ChatGPT. They are faster, more powerful, and cheaper to

Bringing it all together

Individually, all these areas will undoubtedly progress in the coming years. What is incredibly exciting is the possibility of AI carrying out full design-make-test cycles using in-built reasoning processes. Indeed, the first very simple examples have recently been shared on ArXiv (an open access repository of articles) by a group of researchers from the Laboratory of Artificial Chemical Intelligence, National Centre of Competence in Research Catalysis, and the University of Rochester, UK, using an LLM to plan and carry out the synthesis of some simple small molecules. Giving LLMs access to the relevant tools for tasks such as simple data analysis may free up time for scientists to carry out more detailed, in-depth, or creative tasks.

There is certainly a great deal of promise for AI in drug discovery, but there are also areas that need to be improved. Data standardization can enable us to build larger interoperable



data sets for AI to train on, improving models and helping build the necessary supporting computing infrastructures. For example, a general trend towards cloud-computing architectures will enable resource scalability.

Increasing trust in the reliability of AI tools will only come with time and evidence. Open science and an increasing number of publications will support this (as will educating potential users on how these methods work) and provide clarity on the strengths

and weaknesses of different AI methods in particular scenarios.

Increasing ease-of-use by embedding AI tools within intuitive workflows and visual interfaces will also support adoption. Allowing users to access AI as part of an integrated in silico development pipeline containing all the tools and data they need could have significant impacts on efficiency. Each update, coupled with the continuous improvements in AI methodologies themselves, could have a revolutionary impact on the efficiency of drug discovery pipelines.

Pharma's Portal to the Lab of the Future

Labs of the future will use VR, AR, AI and more. But we must overcome the barriers of implementation, including cultural resistance.

By Becky Upton, President of The Pistoia Alliance

The Pistoia Alliance was founded more than 15 years ago as a not-for-profit with the mission to lower barriers to innovation in the life sciences through pre-competitive collaboration. Core to this mission is working with our member organizations to overcome common obstacles that are holding back technological innovation in our industry. We know that adopting new technologies in R&D and proving their value is both a huge undertaking and a great expense. By working together, we are able to break down silos and remove the interoperability problems often created when companies choose to “go it alone,” allowing our members to integrate emerging innovations more seamlessly and continue delivering life-changing therapies to patients.

The “lab of the future” is one such area where we are keen to see more innovation. To see how our members are progressing with integrating new technologies into the lab, we worked with the Lab of the Future Congress to survey experts from top pharma companies, medium enterprises, startups, and beyond. Our survey reveals which technologies are top of the investment agenda, what organizations are struggling with, and how we can help make the tech of tomorrow a reality in the labs of today. Over half the experts we surveyed said their labs are already using robotics; 40 percent said they expect to be using virtual reality, augmented reality, and wearables in the next two years. AI and

machine learning also feature highly in the adoption curve, with AI seen as being able to significantly accelerate existing workflows in small molecule discovery and lead optimization for new drug candidates. Given this proven potential, it's not surprising that AI and ML topped the list as the technology most companies (60 percent) plan on investing in during the next two years.

Underpinning the successful use of any new technology in the lab, however, is the need to establish a foundational data backbone. What does that mean? Well, all the behind-the-scenes, less headline-grabbing systems and data science techniques that are critical to unlocking the benefits of AI and machine learning. For example, cloud technologies that provide storage space and computer capacity are being invested in by more than half of companies, while 60 percent expect to be using laboratory information management systems (LIMS) in the next two years to digitally capture and share methods and results. Such foundational data management technologies can lay the groundwork for more hyped-up technologies, such as generative AI. After all, companies must learn to walk before they can run.

Despite encouraging investment in foundational data technologies, the survey also revealed there are still significant data quality and management challenges that prevent companies from realizing a return on their investments. For example, data silos were cited as barriers by 66 percent of respondents, followed by unstructured data (58 percent), and lack of metadata standardization (42 percent). These insights suggest research environments continue to be what we call “unFAIR” (findable, accessible, interoperable, reusable), preventing data from moving freely through the research environment – and thus leading to longer, more costly workflows.

The other barrier called out by almost half of respondents was cultural resistance – specifically, hesitancy over data sharing. And that's despite the industry now generally acknowledging that sharing expertise is essential for overcoming regulatory and ethical hurdles, mitigating risk, and



preventing duplication of costly R&D work. A third of our experts also pointed to a lack of proven business cases for senior stakeholders, such as time saved by using LIMS, or number of new targets identified by AI. Though labs continue to adopt new technologies at pace, measuring and proving the value of technology with such tangible business case studies is important for fuelling further investment.

The good news is there are some steps that can be taken to overcome common barriers and ensure researchers, investors, and patients can all reap the benefits of more efficient drug discovery brought about by technology. Some of the resources and actions our respondents called for include:

- Best practice use cases that demonstrate the value of AI (55 percent) and FAIR implementation (43 percent).
- Data governance principles/frameworks for AI (32 percent) and FAIR implementation (40 percent).
- AI algorithm skills training (38 percent).

- Management of data standards and ontologies for FAIR Implementation (42 percent).
- Maturity models to benchmark FAIR implementation against other companies (31 percent).

What all our experts' suggestions have in common is a clear need to collaborate, share knowledge, and share risk. If companies come together, the industry can collectively reap the benefits of the labs of the future – improving the accuracy and reproducibility of research, preventing duplicated efforts, reducing long term costs, and more besides.

Since its inception, the Pistoia Alliance has been making headway on some of the above suggestions through our member-led projects and new training initiatives. We are shaped by the priorities of the life sciences community and our members, and we invite organizations to bring ideas to us today so we can realize the journey to the lab of the future together.

Drug Discovery's Digital Future

From AI to integrated in silico systems and less reliance on animal testing; we ask an expert from Elsevier about the future of digital tech in drug discovery

Historically, the translation of new medicines from the preclinical to the clinical stages has relied on manual, time-consuming processes that have a high rate of failure – 93 percent of drugs entering clinical trials do not secure regulatory approval. Researchers can spend months gathering data from numerous scientific articles on the potential toxicity of their drug, as well as its potential adverse events, dose selection, and how it compares to other drugs on the market. This data is then spread across different sources internally and externally, and in varied formats.

A need therefore arose to design a platform to provide this data in a single place, and in a standardized and interoperable format. When PharmaPendium was launched in 2009, its primary function was to help pharma companies increase the success of their regulatory submissions so more new treatments could reach patients sooner. Regulatory documents have always been core to PharmaPendium but, in its latest version, Elsevier and the FDA have collaborated on digitizing

regulatory content, including labels, summary approval packages, and Advisory Committee Meeting documents.

The datasets produced need to be efficient enough to be machine readable and available for off-platform use so researchers can quickly embed data into their workflows. Packaging data in this way is now enabling pharma companies to safeguard their investments by making faster, more informed decisions about what drug candidates to advance. Olivier Barberan, Director of Translational Medicines Solutions at Elsevier, tells us more about the platform – and offers a glimpse into the future of drug discovery and development.

How can the platform help the drug discovery process?

Data analysis that would have taken months typically now takes half a day with the packaged data in PharmaPendium.

The search, analytics, and predictive capabilities in the platform help accelerate drug development approvals, including drug safety tests, clinical trial design, and post-market surveillance. We specifically designed the tool to be as user friendly as possible. For example, the quick search bar facilitates search across a range of information from quantitative data to full text. Users can navigate through drugs, adverse effects, targets, and indications, and refine by relevant datasets including activity, efficacy, pharmacokinetics, or safety.



How is predictive analytics improving translational science?

By using data from previous experiments to refine testing for new drug candidates, predictive tools can enable more efficient, successful regulatory submissions and drug safety assessments. Large datasets of adverse event reports, clinical trials data, medical records, and other literature are used to build computational models that detect patterns associated with adverse drug reactions (ADRs). Advanced algorithms are then used to develop predictive models and risk scores for specific ADRs, so companies can screen out unsafe candidates at the earliest possible stage and advance the most promising.

We've also developed our own Drug-Drug Interaction (DDI) Calculator, which can be used before first-in-human studies to avoid the entire phase I arm of a clinical study by predicting harmful DDIs. Sanofi/DNDi used the calculator during approvals for fexinidazole, a drug for sleeping sickness. The results of in vivo simulations were used to characterize the risk of interaction of fexinidazole with co-medications in the drug interaction and PK sections of its labeling. Sanofi/DNDi included these predictions in the dossier it submitted to the agencies, and gained regulatory approval with the FDA and EMA, as well as in the Democratic Republic of Congo and Uganda.

How can these types of tools help reduce animal testing?

Elsevier is actively developing tools that support the “three Rs” framework to replace, reduce, and refine animal testing. We recognize that technology – in particular, predictive analytics – will play a key role in modernizing how drugs are tested, as outlined in recent changes to the FDA Modernization Act.

The data provided in PharmaPendium reduces the need for excessive testing by allowing toxicologists to analyze past studies with similar drug indications to choose the right option the first time. It's even possible to replace animal testing at some stages of secondary pharmacology with the aforementioned Safety Margin Tool; for example, the tool calculates the risk of off-target ADRs based on past in vitro results, so far fewer tests are run on animals during this stage.

Could animal testing one day be a thing of the past?

The life sciences industry and regulators have made great progress globally in the move away from animal testing. For example, the EU's 2013 ban on animal testing in cosmetics, or 2022's FDA Modernization Act, which legitimizes the replacement of animal models with cell-based assays, organ chips, and computer models. The industry is generally beginning to recognize that animal models don't accurately mimic how the human body responds to drugs, chemicals, or treatments.

Despite progress, it's hard to say when the practice will be fully eliminated. Patient safety is absolutely paramount, and proving alternative tests are reliable will require the scientific community to continue refining and validating these methods before they can gain regulatory acceptance. Almost all major regulatory agencies would need to change their safety and efficacy assessments, a legality that will take time and consideration, followed by a transition period for companies. Though complete elimination may not happen in the very near future, gradual changes and significant reductions in animal testing are likely to continue at pace.

Is pharma getting on board with new tools and technologies?

Pharma companies are increasingly investing in data technologies and predictive tools, with more than half of labs using AI technologies. The majority of large pharma companies, as well as the FDA and PMDA, are using digital tools to support drug development and regulatory submissions. Smaller pharma also stand to benefit from such tools, because these companies often only have one or two team members responsible for gathering information for toxicology reports or regulatory submissions – a job that would be handled by a team of five to 10 people at a large company. Having searchable datasets and predictive analytics tools could hugely streamline the workloads of these smaller teams, as well as provide a more thorough, accurate search than could be done manually.

What does drug development look like in the future?

In the future, drug development will be driven by an integrated in silico system that will simulate the human body – so-called “digital twins.” Currently, digital twin technology is more suited to specific, targeted purposes. For example, modeling the absorption of a drug to establish the therapeutic window of individual patients. In other words, how long a drug is effective in a person.

We do not yet have the quality of data to address every variable in the body to create an accurate full body digital twin, but once we have enough accurate and reliable data it could become a reality in a decade, enabling us to model reactions at speed without involving humans or animals. So, when there is a public health crisis, we can use data already available, with no risk to life, to understand the disease and how it interacts with already approved drugs to start fighting it as quickly as possible.

In the meantime, the industry should focus on the here-and-now capabilities of digital twins, as the technology could still have a huge impact on current healthcare challenges, such as treating chronic disease and pain management.



SHOWTIME IN FRANKFURT: *Achema 2024*

Coming to Frankfurt,
Germany, June 10-14,
Achema will showcase
technologies and services
in the process industries,
including chemical and
pharma engineering,
biotech, environmental,
and more

Credit: DXR, CC BY-SA 4.0, via Wikimedia Commons

Top themes at this year's show include digital, green, lab, pharma, process, and hydrogen. According to the Achema program, "These themes shape the future of the process industries by driving innovation towards sustainability, efficiency, and flexibility. They encourage the industry to adopt new technologies and approaches that reduce environmental impact, optimize resource use, and enhance product quality and safety."

You likely won't need reminding that Achema is big. The trade exhibition boasts over 2,700 exhibitors, while the Achema congress delivers over 900 lectures and panel discussions. There are also plenty of side events, including the International Powder and Nanotechnology Forum, Flow Chemistry Symposium, AIRA Robotics Challenge, Career Day, and much more.



THE BASICS

Opening hours

Monday, June 10 through
Thursday, June 13

09:00 – 18:00 for visitors
(08:00 – 19:00 for exhibitors)

Friday June 14

09:00 – 16:00 for visitors
(08:00 – 19:00 for exhibitors)

Tickets

- Employees in industry, trade, and commerce: 90 EUR (full event) or 40 EUR (day)
- Employees in universities, public authorities, and associations: 60 EUR (full event) or 40 EUR (day)

A LITTLE HISTORY LESSON

ACHEMA's founder, Max Buchner, dreamed up the exhibition in 1918 as a way to connect chemistry and engineering, which at that time remained two separate worlds. His grand idea arrived right after the defeat of the German Empire in World War I, and its realization came in 1920 at the dawn of the Weimar Republic – a new, open, and exciting German democracy. ACHEMA kept running through the Weimar period. 1926 saw the setup of a parent company named DECHEMA, and ACHEMA's sixth iteration in 1930 attracted the event's first international attendees. ACHEMA continued to run after Hitler took power in 1933, but was dealt a blow when the DECHEMA Frankfurt headquarters were destroyed in 1944 – a year of multiple allied bombing raids on the city. The next year, the US 5th infantry and 6th armored division showed up and captured the city in four days.

The first postwar ACHEMA was held in Festhalle in 1950. Here, we would direct readers to the ACHEMA website where they can enjoy a few hip and/or groovy photographs of the event and its attendees in the first postwar decades. In the shot for 1973, we see three ladies dressed in styles very much of the decade, surveying some equipment. The ACHEMA site captions the photo "Diversity," and notes that the women in the photograph won't be limiting themselves to the "ladies program." We've come a long way, haven't we?

The late seventies and eighties saw some interesting ACHEMA traditions spring up: "India day," and the opening of the event by a live orchestra playing the overture to Wagner's *The Master-Singers of Nuremberg*.

PICK OF THE PROGRAM

As noted, hundreds of lectures will take place over the four-day event, but here are some highlights we've picked out of the schedule:

Monday, June 10

AIRA Robotics Challenge (Hall 11.1, Stand A5)

If you're interested in robots then this challenge is worth checking out. Teams will be demonstrating how robots can perform tasks in mock plant and lab scenarios, with a focus on systems that enable remote control.

10:30–11:00 (Facette - 3 via)

Designing Tomorrow's ATMP Facility: How to Leverage Emerging Technologies

How do you right-size your operations? Niranjan Kulkarni and Nicolas Bahler from CRB share their tips and offer two case studies for consideration.

13:00 - 14:00 (Europa - 4.0)

Next generation pharma manufacturing – current advances in cell and gene therapy

The Achema organizers invite attendees to this session to “meet leading experts from academic and industrial research who share their insights into all stages of the development and production of cell and gene therapies.”

14:30 - 15:00 (Facette - 3 via)

Advancing Cell and Gene Therapy Manufacturing with integrated

manufacturing platforms

Hear from Miltenyi Biotec's Silvio Weber on the challenges presented by cell and gene therapies – and how integrated manufacturing can be implemented.

Tuesday, June 11

From 9:45 (Hall 4.C, Room Alliance)

International Powder and Nanotechnology Forum

On Tuesday, there will be sessions on nanotechnology and simulation; Wednesday will include presentations on pharmaceutical process engineering and materials, and drug delivery systems with nanotechnology.

14:00 - 14:30 (Zeta Pharma Innovation Stage - 4.1)

Technology, innovation and intelligence: paving the way for Pharma 5.0

Looking at the future of pharma's supply chain and the role that AI and data-driven approaches will play

14:30 - 15:00 (Facette - 3 via)

Sustainability – Reduce, Recycle and Reclaim strategy for Water in Pharma Manufacturing Through Decarbonization

The speaker suggests strategies for achieving sustainability in pharma manufacturing by focusing on Earth's (arguably) most valuable asset: H2O.

15:30 - 16:00 (Zeta Pharma Innovation Stage - 4.1)

From Paper to Hardware a Technology Perspective on EU GMP Annex 1 (2022)

The EU GMP Annex 1 was finally published in August 2022. This presentation focuses on technical measures to support compliance.

Wednesday, June 12

11:00 - 11:15 (Zeta Pharma Innovation Stage - 4.1)

Precision for Automation, Driven by Data – RTLS Use Case in Pharma

This short presentation featuring speakers from Siemens and GSK will look at how the big pharma company is using intelligent and real-time data to optimize efficiency and drive business value.

15:00–15:30 (Zeta Pharma Innovation Stage - 4.1)

Current Developments and Challenges in Pharmaceutical Parenteral Packaging and Labeling: Addressing the Growing Need for Small-Batch Production and Embracing Digitalization and Cutting-Edge Technologies
Lars Skole from LSS offers tips on how pharma manufacturers can address parenteral challenges.

15:30 - 16:00 (Symmetrie 3 - 8.1)

Continuous manufacturing, the goals and benefits from a customer perspective

Case studies will show how companies met goals and business drivers by implementing continuous manufacturing and flow chemistry.

16:30 - 17:00 (Facette - 3 via)

Effectiveness and Benefits of Robotic

Airborne Disinfection System Clean Rooms

Learn about a study involving a robotic airborne disinfection system combined with 7.4% hydrogen peroxide.

Thursday, June 13

From 10:00 (Foyer 5.1 and 6.1)

Career Day

Featuring a job board and the opportunity to network to find new opportunities, whether you are a young professional or seasoned industry veteran.

14:00 - 14:30 (Lab Innovations Stage - 12.0)

Plastic in the Lab: What Are the next steps?

Expert from Eppendorf looks at the problems of plastic-based lab consumables and what new materials might be on hand to help.

15:00 - 15:30 (Zeta Pharma Innovation Stage - 4.1)

Single-Use Technology Project management – CAPEX versus OPEX

How the increasing trend towards single use affects facility design – and what parameters need to be evaluated to make the right choice.

15:30 - 16:00 (Zeta Pharma Innovation Stage - 4.1)

Improving the Sustainability of Pharmaceutical Freeze Drying
Lyophilization is a time and energy-intensive process – but new innovations are helping make the process more sustainable.

AND AFTER WORK...

Kick off

If you're a soccer/football fan, you're in luck. The European Football Championship kicks off on June 14. Five matches will be held at Frankfurt Arena, with the first, Belgium versus Slovakia, taking place on June 17. There will also be a 1.4 km fan zone on the banks of the Main. All 51 games will be broadcast on screens – including a floating 720-inch screen close to Friedensbrücke bridge.

Before the championship kicks off, there will be an audiovisual opening production on June 12 at the Flößerbrücke. The eastern side of the bridge will be lit up with sound choreography, with the skyline as a backdrop.

City tours

If sport isn't your thing, how about a city tour? Tours of the old town

take place daily on foot at 11:00 and 14:00, lasting around 90 minutes.

Google #visitfrankfurt city tours for more information. Boat trips are also available.

Famous landmarks

Palm Garden (Palmengarten)
Senckenberg Natural
History Museum
Main Tower
Old Opera House (Alte Oper)
Carmelite Monastery

More unusual landmarks

The Pinkelbaum (the peeing tree) is located in Frankfurt's national forest. And yes, it's a tree that pees.

"Crashed train" subway entrance (Bockenheimer Warte U Bahn) is designed to resemble an old-fashioned tram carriage that has sunk into – or is emerging from – the earth.

Credit: Pexels



Oligonucleotides: Getting Equipment Selection Right

The oligonucleotides market is growing rapidly, with drug developers increasingly attracted to this intriguing drug modality. But manufacturing can be challenging – and choosing the right equipment for the job is essential. Established suppliers – such as Asahi Kasei Bioprocess (AKB) – can not only provide valuable guidance on equipment selection based on your process but also help guide further optimization when producing these complex therapeutics.

Featuring Tom Krebstakies, Sales Manager for Europe and Asia at Asahi Kasei Bioprocess Deutschland GmbH in Cologne, Germany

Why are oligonucleotides such a hot topic in drug development?

Oligonucleotide therapeutics are characterized by high efficiency and high specificity. They can directly target the site of action, such as the regulation of gene expression, and have great potential for treating metabolic diseases, genetic diseases, and cancer, as well as preventing infectious diseases.

The science, production, and commercialization of oligonucleotides have all advanced quickly in recent years – and the global market has developed tremendously. The global oligonucleotide synthesis market was valued at around \$7 billion in 2023 and is projected to potentially double or triple by 2030. The calculated

CAGR is therefore easily >12 percent during the forecast period. Though delivery into the target cell has historically been a challenge, platforms have now emerged, such as LNPs or GalNAc conjugates for siRNAs for liver delivery. Now, the focus is also on developing delivery solutions for very specific tissues and cell types, opening avenues to tackle a broader range of diseases.

As anything grows, scaling up manufacturing processes and capacities becomes a major topic. Priorities include modernizing facilities, optimizing machinery, and implementing more efficient synthetic processes. At the same time, there is also a need to consider sustainability. Oligonucleotide manufacturing processes are connected to a certain amount of waste; for example, 1 kg of product requires 1000 kg of acetonitrile. Finding ways to reduce waste is obviously better for the environment and the planet, but can also connect to improved production efficiency and cost control. The



industry is working on optimizing existing technologies and developing new approaches to reduce waste and byproducts. Digitalization, automation, and Pharma 4.0™ will be important for both scalability and environmental care. A better understanding of processes will also help guide optimization and create the ideal synthesis.

What is the manufacturing process for oligos?

The most widely used state-of-the-art process is solid phase oligo synthesis. The synthesizer controls the reoccurring four-step cycle of detritylation, coupling, capping, and oxidation. The reaction occurs in synthesis columns, while the synthesizer precisely delivers the amidites and all required reagents. The sizing and pairing of the synthesizer with the columns are key

for effective coupling and yield.

Every cycle, a phosphoramidite is added to the growing and immobilized oligonucleotide chain. Once finalized, the oligo is then cleaved from its solid support and protecting groups are removed to obtain an active API. This step is recommended to be automated using a cleavage and deprotection system, ensuring optimized conditions for high efficiency.

The downstream phase starts with purification (reversed-phase, anion exchange, or hydrophobic interaction chromatography) to remove undesired shortmers and impurities. Also in this step, the use of dedicated medium pressure liquid chromatography systems with matching dynamic axial compression columns is imperative for efficiency and high-quality yields. Auxiliary components and features are available to increase handling, safety, and process efficiency. After purification and before lyophilization of the end-product, the oligos undergo the process of desalting by buffer exchange and concentration. For this application, AKB recently launched an ultrafiltration/diafiltration (UF/DF) system intended for use in oligonucleotide manufacturing environments that require specific safety directives.

What are the biggest considerations and challenges when setting up a new manufacturing line?

From our perspective as a technology supplier, we recommend considering scalability, as well as the integration into the facility and the overall production approach. Is the production line intended for one product? Or is the line for a CDMO producing multiple products where the highest flexibility is required?

Because of the complexity of scale-up, partnerships and collaboration with organizations that have the right expertise and technological solutions can be beneficial to make the process faster and easier. The number of variables that need to be considered in both upstream

and downstream processes require more than a “plug-and-play” approach with large-scale equipment.

How should companies approach the challenge of choosing the right equipment?

After determining the right oligonucleotide synthesis type and considering the desired functionality, target application, and cost, carefully evaluate the characteristics of each required step and then select the equipment that best suits your goals. High quality equipment and components play a crucial role in ensuring the efficiency and reproducibility of oligonucleotide synthesis at scale.

All the steps in the manufacturing process require in depth analysis of the parameters, which should be aligned with your process requirements; however, there are a few general features that I can highlight. I recommend looking for an innovative and thoughtful mechanical design that is complemented by automation. Automation speeds up the process steps while ensuring consistency across multiple batches – a prerequisite for reproducible results. Also, choose a system that will allow for seamless transition from small scale to large scale. AKB's systems and columns are specifically designed with scalability in mind, offering a range of sizes that cater to varying synthesis

volumes and throughput demands.

Finally, keep in mind that, though a truly high-performance production line usually requires a higher initial investment, this cost is repaid in long-term impact on operational efficiency and overall cost-effectiveness. Opting for high-quality equipment should result in lower maintenance requirements and less downtime – ultimately leading to higher productivity and cost savings by ensuring synthesis processes run smoothly and efficiently with maximum uptime.

How is Asahi Kasei Bioprocess (AKB) innovating oligonucleotide manufacture?

AKB offers state-of-the-art equipment and components from synthesis through concentration, including the THESYS™ Oligosynthesizer, THESYS ACS Column, THESYS SCS Column, THESYS Cleavage & Deprotection System, CURSIV™ MPLC System, CURSIV DAC Ergo LC Column, SLURIPREP™ System and VANTIJ™ Ultrafiltration/Diafiltration TFF System. All our products are “built for you” to ensure that a customer's individual requirements are met. The ability to use the same equipment to manufacture different products with different chemicals or at different scales eliminates the need for costly new investment or reconfiguration of equipment.

AKB relies on user familiarity with the cross-platform components of all systems. Devices and components are designed to work together seamlessly in a single integrated system, minimizing compatibility issues and ensuring optimal performance and efficiency. This also applies to the OCELOT® system control for all automated system types, which is an intuitive, powerful software platform that can be integrated into plantwide control systems. That said, the operator is certainly not disregarded; rather, the operator is always considered in the ergonomic design of a system, to

enable increased efficiency and safety.

With 30 years of experience in various areas of biopharma manufacturing, AKB can apply technical principles precisely to the requirements of different drug modalities – or rethink them to develop innovative products. Our strength is the ability to apply our expertise and experience individually in every project to achieve the best possible results – together with the customer. Close collaboration strengthens relationships and communication channels. As a trusted advisor, we encourage interaction with project managers, engineers, and service during and after successful project completion.

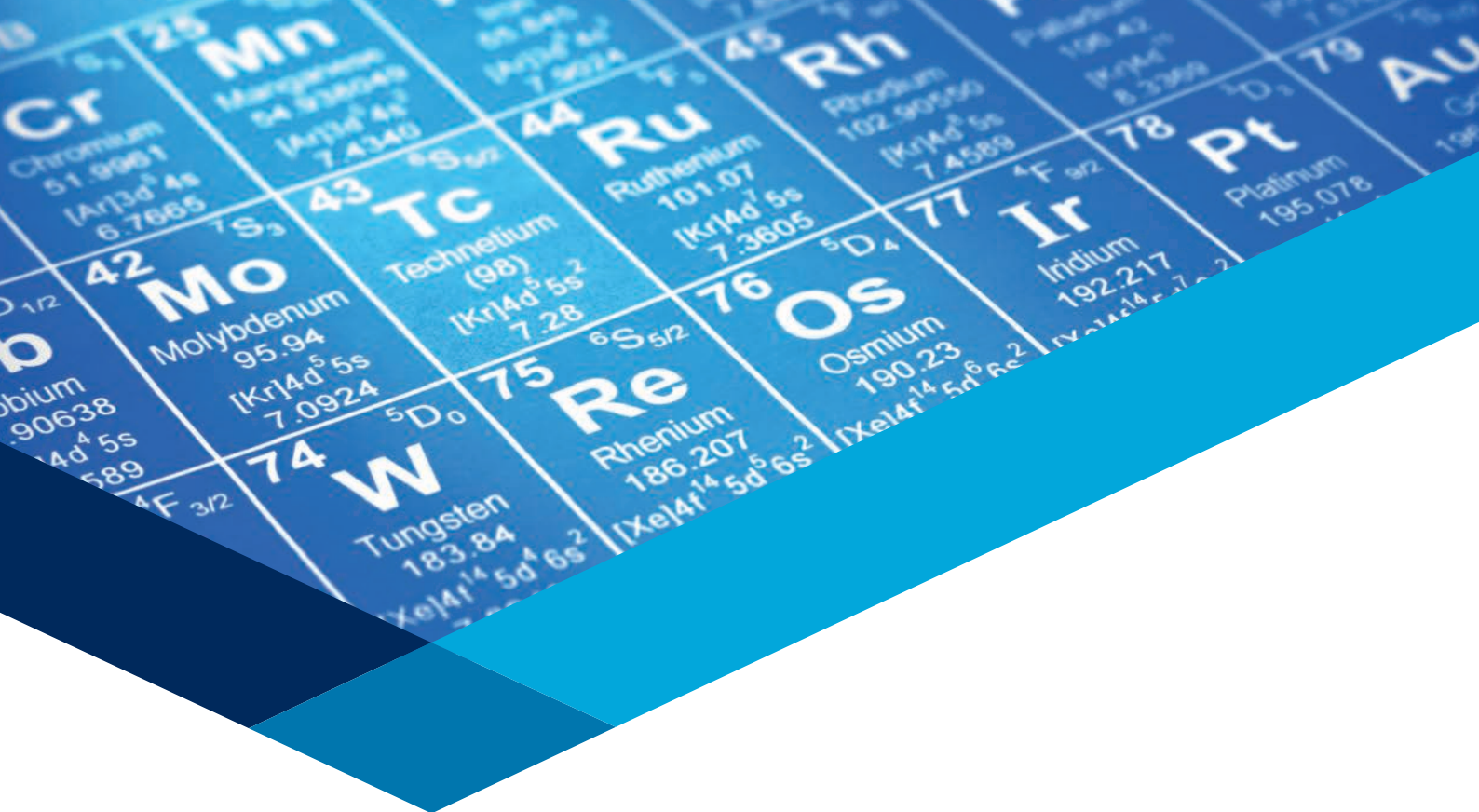
What advice can you offer to manufacturers that are just getting started with new lines and investments in the oligo field?

Make sure you have a clear understanding of the oligonucleotide synthesis process before purchasing equipment or components. And choose a supplier that has a comprehensive range of equipment – and don't forget to consider their customer support. A good supplier should have exceptional customer support that ensures smooth procurement and ongoing help with any issues that arise, including advice on improving efficiency and maintaining compliance with industry standards.

To ensure long-term cost efficiency, evaluating the cost of initial equipment and operations is a given, but you'll see greater benefits if you are willing to collaborate with partners that can help you take performance and efficiency to another level – and in a future-proof way.

AKB's experience in oligo scale-up and the comprehensive portfolio of flexible, future-ready technologies – combined with a breadth of technical expertise and end-to-end support – make the company an ideal partner to quickly navigate the complex challenges in this exciting and rapidly growing therapeutic space.





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Core Topic Cell & Gene

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Pfizer gene therapy. Pfizer has received FDA approval for its one-time gene therapy Beqvez to treat adults with moderate to severe hemophilia B. Beqvez helps patients produce FIX internally and could eliminate the need for regular prophylactic infusions. For now, however, the therapy is exclusively authorized for use in patients who currently use FIX prophylaxis therapy, have current or historical life-threatening hemorrhage, or have repeated and serious spontaneous bleeding episodes. They must also not have neutralizing antibodies to adeno-associated virus serotype Rh74var. The price will be \$3.5 million in the US – the same price as Australian drugmaker CSL's rival gene therapy Hemgenix. Pfizer is also reportedly launching a warranty program based on durability of patient response to treatment.

Long live CAR T cells. Given that less than 50 percent of patients who receive CAR-T cell therapy remain cured after a year, advancements in our understanding of the underlying biology behind memory T cells are crucial to the ultimate goal of progress. Building on this urgency, cancer scientists at Stanford and the Children's Hospital of Philadelphia discovered that the FOXO1 protein improves the survival and effectiveness of CAR-T cells (DOI: 10.1038/s41586-024-07300-8). In a press release, senior study author Crystal Mackall said, "These findings offer new

insight into a critical question around CAR-T cell therapy. This insight could lead to stronger CAR-T cells and the ability to help more patients."

New frontiers. Walgreens, one of the largest retail pharmacy companies in the world, has announced plans to launch a variety of new services as a part of its newly integrated specialty pharmacy business, including a licensed facility in Pittsburgh dedicated to cell and gene therapy services. The 18,000-square-foot center will help drugmakers and health-care providers navigate the complex supply chain for those treatments and manage patient needs, among other issues.

Treatment equality. Penn Medicine researchers recently explored whether patients treated for B-cell non-Hodgkin's lymphoma who are part of minority populations have equal access to CAR-T cell therapies or not (DOI: 10.1056/EVIDoa2300213). Specifically, they assessed the percentage of ethnic groups – defined by the federal government as a minority – treated for large B-cell lymphoma and the percentage who received CAR-T cell therapy at two different cancer centers between 2018 and 2022. The team concluded that access to tertiary centers for large B-cell lymphoma care was preserved but access to commercial CART19 immunotherapy appeared to be reduced, calling for further research.

IN OTHER NEWS

Pfizer pauses Duchenne muscular dystrophy clinical studies after death of patient.

The National Institutes of Health awards Sangpil Yoon, a University of Oklahoma engineering researcher, a \$2.3 million grant for a gene therapy delivery system.

Astellas Pharma opens \$90 million, state-of-the-art cell and gene therapy center in South San Francisco.

Ferring Pharmaceuticals and SK pharmteco announce agreement to scale up commercial manufacturing capacity for intravesical gene therapy for adult patients with high-risk Bacillus Calmette-Guérin.

Researchers at UC San Francisco receive grant up to \$11 million to fund a clinical trial that uses CAR-T guided by precision technology to treat people with glioblastoma.

Open or Closed?

How to find the right balance in cell therapy manufacturing

By Krishnendu Khan, Senior Scientist, R&D, at West Pharmaceutical Services

As the demand for cell-based therapies continues to grow, the industry must explore current and future fill-finish packaging strategies. Understanding the advantages and challenges associated with different modes for cell therapy packaging will allow drug manufacturers to choose the most suitable system.

Chimeric antigen receptor (CAR) therapies, as a treatment avenue for various cancers, are gaining in momentum. Current approved therapies are mostly autologous in nature, which ensures no immune rejection of the drug product. However, as demand for CAR-based cell therapies increases, we'll see the current manufacturing process become untenable due to its small production scale, high costs, and the time required for each "batch."

These, and other challenges, are pushing scientists to develop a new generation of cell-based therapies that are allogeneic in nature with "off-the-shelf" options. To make such cell therapies accessible, a complete overhaul of manufacturing is needed as current processes are not equipped for large batches.

Autologous CAR therapies are produced through "closed" processing where the drug substance (cells extracted from patients) is isolated in a manufacturing unit that provides a controlled and sterile environment

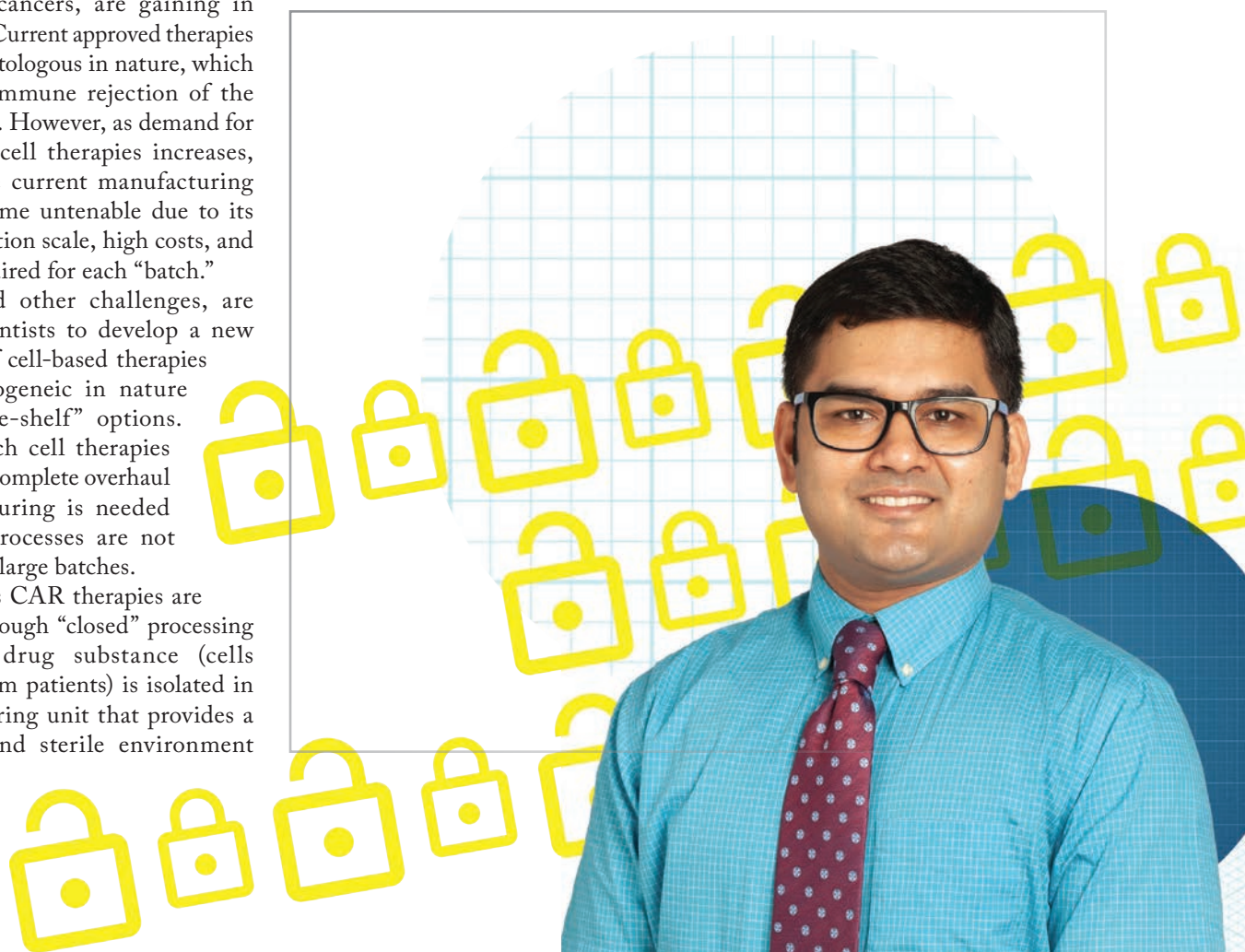
throughout production, formulation, packaging, and storage, as well as transportation. This approach has several advantages, including minimizing the risk of contamination and protecting the drug product from external pathogens.


But cost is an issue; such closed systems use containment technology that requires specialized equipment and infrastructure, often leading to higher capital and operational costs. Two approaches are currently followed: i) the use of modular equipment, where each piece of equipment is used for a single unit operation, such as cell isolation following apheresis, genetic manipulation, expansion followed by harvest, and final drug product formulation, or ii) all-in-one, end-

to-end equipment that encompasses the entire process and uses single-use consumables.

Both approaches have their own advantages and pitfalls. Irrespective, as manufacturing needs increase (as will be the case with allogeneic therapies), the use of any equipment must be optimized. Moreover, monitoring critical parameters, such as cell viability or cell count, may require additional sampling or sampling ports that can introduce risks of contamination, essentially, "opening" the process.

Adaptability is another issue associated with closed fill-finish. Current CAR cell therapy manufacturing is designed around T-cells – the first (and relatively unchanged) cell type to be used. But the fixed design and infrastructure of





closed fill-finish systems limits their compatibility with the evolving cell therapy landscape that requires the use of different cell types, including NK cells and macrophages. Modification or upgrades to the closed system may require additional validation and regulatory approval, leading to delays and increased costs. Moreover, the scalability of closed systems is limited because of constraints in equipment size or manufacturing capacity, and may require significant investments in additional closed systems or facility modifications as demand increases.

Although closed fill-finish is the way the cell therapy industry currently operates, we need to identify other solutions that allow for better scale up of the manufacturing process. To that end, we could consider an open fill-finish process, such as what we see with monoclonal antibodies. A primary advantage of this approach would be its flexibility in terms of scalability for allogeneic therapies. However, open fill-finish comes with inherent risks, such as increased likelihood of contamination, as well as the requirement for strict aseptic techniques, environmental controls, and highly trained personnel.

When discussing fill-finish, we also need to consider the final packaging container – usually a cryo-bag for cell therapy.

These are adopted because of their

proven use as containers for blood-based infusion products and also their compatibility with closed fill-finish equipment. But there are various challenges associated with cryo-bags, including bag-breakage at ultra-cold temperatures and the problem of dead-volume, which can lead to dosing errors. Moreover, the requirement for additional packaging material,

“Although closed fill-finish is the way the cell therapy industry currently operates, we need to identify other solutions that allow for better scale up of the manufacturing process.”

like over-wrap bags and aluminium cassettes, along with racking systems for storage and transportation, increases the overall price and complexity.

One alternative to cryo-bags is rigid vials, which offer many advantages and are compatible with open aseptic fill-finish processes. Rigid vials provide excellent protection and stability for cell therapy products, with the hermetic sealing of vials providing an effective barrier against microbial contamination while helping to maintain sterility of the product throughout its shelf life. Rigid vials are also more suited for freezing, and can withstand long-term storage in the ultra-low temperatures required for cell therapies without affecting vital container closure integrity. Moreover, rigid vials have been used for a long time

for other temperature sensitive therapeutics, such as monoclonals, so their use in cell therapy aligns with established industry practices and regulatory requirements facilitating the approval process. The compatibility, real time monitoring capabilities, sterility assurance, process development benefits and precedence of regulatory acceptance makes rigid vials well-suited for open fill-finish of cell therapy drug products.

The decision isn't simply open or closed; it may also be possible to adopt a hybrid approach, where earlier steps of manufacturing are kept closed whereas the final fill-finish steps are done aseptically to gain the best of both worlds.

The choice between closed and open fill-finish for cell therapy drug products ultimately involves a careful balance between safety, accessibility, efficacy, and the type of cell type used. Closed manufacturing and fill-finish offers robust protection against contamination and environmental factors ensuring integrity of therapeutic cells; open aseptic fill-finish on the other hand provides greater flexibility and a route to scale up, which will be critical in the future as demand for therapies grows. By leveraging the advantages of both approaches, researchers and clinicians can optimize the safety, accessibility, and efficacy of cell therapies.

Changing Regulation Around ATMPs in Europe

Preparing for the EU's new HTA regulation and Joint Clinical Assessment process

Starting in January 2025, companies looking to bring advanced therapy medicinal products (ATMPs) and oncology products to market in Europe will be required to adhere to the Joint Clinical Assessment process (JCA), as part of the EU's new health technology assessment (HTA) regulation. The assessment aims to harmonize processes and evidence requirements for manufacturers through a single clinical test – intentions revealed by the European Commission in the recent JCA framework. However, questions remain over how the process should run, what companies need to do to prepare for it, and how ATMP developers can prioritize joint scientific consultations.

We spoke with Herbert Altmann, vice president, pan-european market access and healthcare consulting, and Lung-I Cheng, vice president and head of cell & gene therapy service line, both at Cencora (formerly AmerisourceBergen), to learn more.

What do ATMP developers need to understand about the EU's new HTA regulation and, more specifically, the JCA process?

Health technology assessments — which mandate formal documentation and evidentiary requirements — play a vital role in determining whether a product approved by the EMA is reimbursed and accessible in the market. Assessing the clinical benefit of a product is a critical part of the HTA process, but the criteria used to assess new pharmaceuticals varies widely across Europe.



As part of the EU's Regulation on Health Assessment Technology, the JCA wants to streamline the clinical assessment of new pharmaceuticals and medical devices across member states to reduce redundant practices and bring life science innovation faster to patients in Europe.

The implementation of the JCA process will occur in phases, with the first phase commencing on January 12 2025. Initially focusing on oncology drugs and ATMPs, this new process will be mandatory. And, given the tight timeline, it is imperative for developers of ATMPs to grasp the intricacies of the regulation and its procedures.

How early should ATMP developers start preparing for the new regulation and the JCA process?

Developers should initiate their internal market access planning for JCA at least 10 months before expected filing with EMA. This timeline allows ample preparation for meeting JCA dossier requirements and developing high-quality package evidence. Ideally, alignment on internal processes should occur prior to designing phase III clinical trials.

Companies need to be familiar with the JCA and Joint Scientific Consultation (JSC) templates, evidence requirements, and timeline. As part of the planning process, developers should prioritize building cross-functional capacity and capabilities. While questions about local HTA processes remain, developers can leverage key learnings from the Joint Action 3 (JA3) pilot assessments to inform their strategy. They can also work with partners to conduct scenario testing, PICO simulation, and consolidation workshops to prepare for the new requirements.

In particular, we believe that the JSC serves as a great opportunity for companies to gain valuable scientific advice, which can

help them develop the best possible evidence package for future HTA assessments — including pan-EU and the individual member states. By participating in a JSC, companies will receive advice from national HTA bodies and the EMA before they finalize their pivotal clinical trial designs.

Engaging with the national HTA bodies is particularly important for ATMP developers, many of which are emerging companies that may not have well-established local market teams.

How will the new HTA impact ATMP approvals?

Though it's still an emerging market, the ATMP sector is entering a new era – with new modalities reaching the market and an influx of new therapies on the horizon, including those that target larger patient populations. There may be as many as six regulatory approvals of ATMPs in Europe in 2024!

The new regulation could optimize patient access to innovative therapies, but this vast undertaking also presents significant complexities to overcome and there remains skepticism and concern that the methodologies won't be fit-for-purpose for ATMPs. The Alliance for Regenerative Medicine (ARM) recently issued a statement, warning the approach – specifically the need for randomised controlled trials – could result in inconclusive JCA reports for many ATMPs.

The lingering questions and concerns, coupled with the tight timeline, underscore the importance of proactive planning. Developers should involve cross-functional perspectives during strategy development and engage partners as early as possible. Through early planning and collaboration, developers can successfully navigate the requirements brought by the new regulation and unlock the potential of their product.



Core Topic Bioprocessing

Credit: Shutterstock

Bioreactor scale up. An open access research paper by Ott et al. (doi: 10.3390/pr12040806) describes efforts to scale fed-batch and perfusion processes “between geometrically dissimilar lab and pilot scale bioreactors.” The authors are from the Zurich University of Applied Sciences, and use a variety of cylindrical stirred lab-scale bioreactors – and successfully scale up to Thermo Scientific’s HyPerforma DynaDrive single-use bioreactor, while also using Repligen’s XCell ATF perfusion systems and single-use devices. The authors wrote, “The scaling of perfusion processes from the 2 L laboratory to the 50 L pilot scale was not only successful but also featured full in-line measurement control.” They also noted that the perfusion process enables cost savings and reduces bioreactor sizes.

New tech on the block. There’s been a number of new product launches recently to help biopharma manufacturers. G-Con has launched a freestanding floorlessPOD for situations when a cleanroom cannot be structurally supported by the host facility, Watson-Marlow Fluid Technology has introduced WMArchitect for single-use biopharma fluid management, and Cytiva has unveiled a single-use magnetic mixer, called Xcellerex, designed for diverse mixing processes.

Sustainable expansion. Fujifilm Diosynth is investing an additional \$1.2 billion to

expand cell culture production at its facility in Holly Springs, North Carolina. The plan is to add 8 x 20,000 l mammalian cell culture bioreactors by 2028 – and will make the site one of the largest biopharma cell culture CDMO facilities in North America. In previously announced investment at the site, the company will also be adding 8 x 20,000 l for bulk drug substance. The investments will also incorporate sustainability initiatives; energy needs for operations are expected to be 100% offset by renewable landfill gas, onsite solar and a virtual power purchase agreement.

COVID-19; all about timing COVID-19 is here to stay, but vaccines will need to be updated periodically to remain effective. Regulators are now putting in place processes for making recommendations about vaccine antigens, including considerations around timings so that manufacturers can act on the recommendations in time to produce vaccines for flu season. To this end, the International Coalition of Medicines Regulatory Authorities (ICMRA) has published a report “Global perspectives on COVID-19 vaccines strain update. Alignment on timing and data requirements,” based on a workshop held in February 2024 featuring WHO and the ICMRA. The goal of the workshop was to “optimise timely vaccine antigen composition recommendations and regulatory approval for vaccines with an updated composition.”

IN OTHER NEWS

RevolKa and La Jolla Institute for Immunology to collaborate on antigens for infectious disease vaccines using protein evolution tech integrated with AI.

TriLink Bio Technologies opens new 32,000 square foot facility for mRNA manufacturing in Sorrento Valley, San Diego.

Lonza introduces service for spray-dried biologics for pulmonary delivery at the kilogram scale from its Bend site in the US.

BioArctic and Eisai sign research evaluation agreement for BAN2802, which combines BrainTransporter technology with an undisclosed drug candidate for Alzheimer’s disease.

Category winners for ISPE’s 2024 Facility of the Year Awards include Eli Lilly Kinsale, Takeda Austria, Zydus Pharmaceuticals, and more; overall winner will be revealed in October.

Five Thoughts: Cell Culture Media

Looking at key milestones, challenges, and innovations in cell culture media – and what lies in store ahead

By Sinan Ozer, Product Line Manager, Media at Corning

Milestones to date

Cell culture media has undergone significant evolution – from simple formulations to specialized and chemically defined compositions. Key milestones over the years include the development of serum-based media, enabling cell growth outside the body. There was later a shift to serum-free formulations, aiming to reduce variability and contamination risks arising from animal-derived components. Further advancements introduced chemically defined media, improving reproducibility and standardization. Recent milestones involve the emergence of specialized media tailored for specific cell types or applications, enabling more precise control over cell behavior and function.

Important considerations

Choosing the right cell culture media includes assessing factors such as cell type, growth requirements, and intended applications. Good media offers optimal cell growth, viability, and reproducibility, and minimizes batch-to-batch variability. It should support desired cell functions and maintain genetic stability.

Choosing inappropriate media can lead to suboptimal cell growth, altered gene expression, or even cell death. This

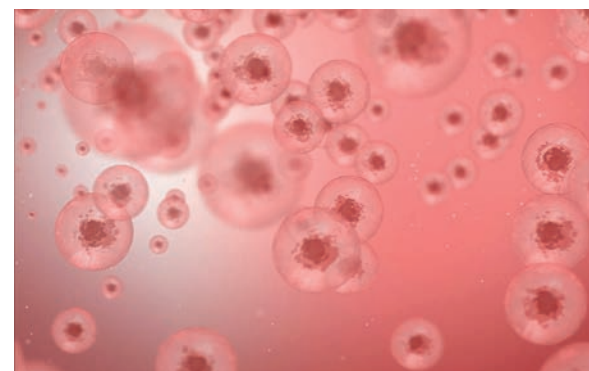
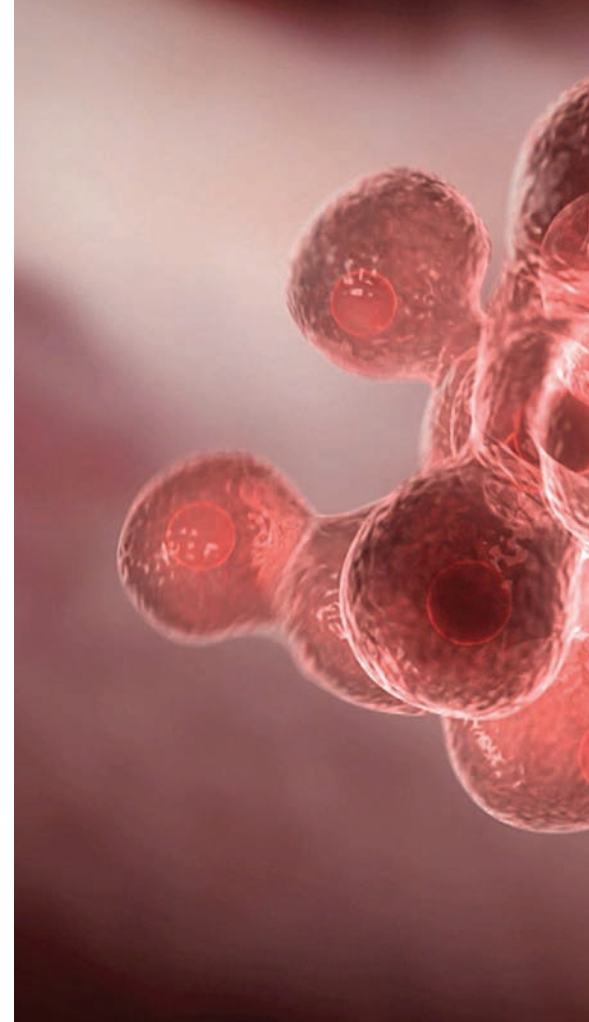
affects experimental reproducibility, leading to unreliable data, prolonged research timelines, and increased costs due to failed experiments.

Common problems

Common mistakes involve neglecting to optimize media for specific cell types, using outdated formulations, or overlooking the impact of media on experimental outcomes. Cells can be cultured successfully by understanding their requirements, regularly optimizing media conditions, staying updated on advancements, and validating media for intended applications.

Other challenges facing drug developers include ensuring media consistency, navigating regulatory complexities, and meeting changing industry standards. And let's not forget the difficulties encountered when scaling up production,

“Advancements include using advanced analytics, machine learning, and bioprocess engineering to develop superior media formulations, improving scalability, and performance.”

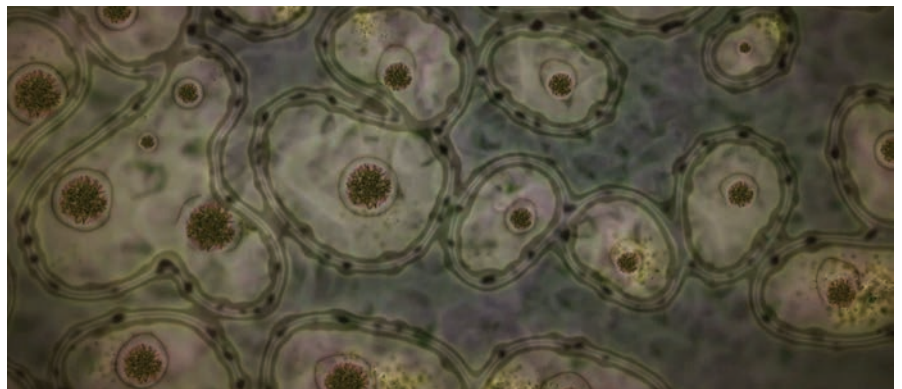
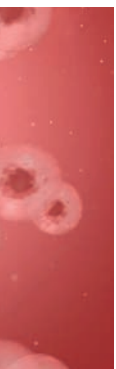
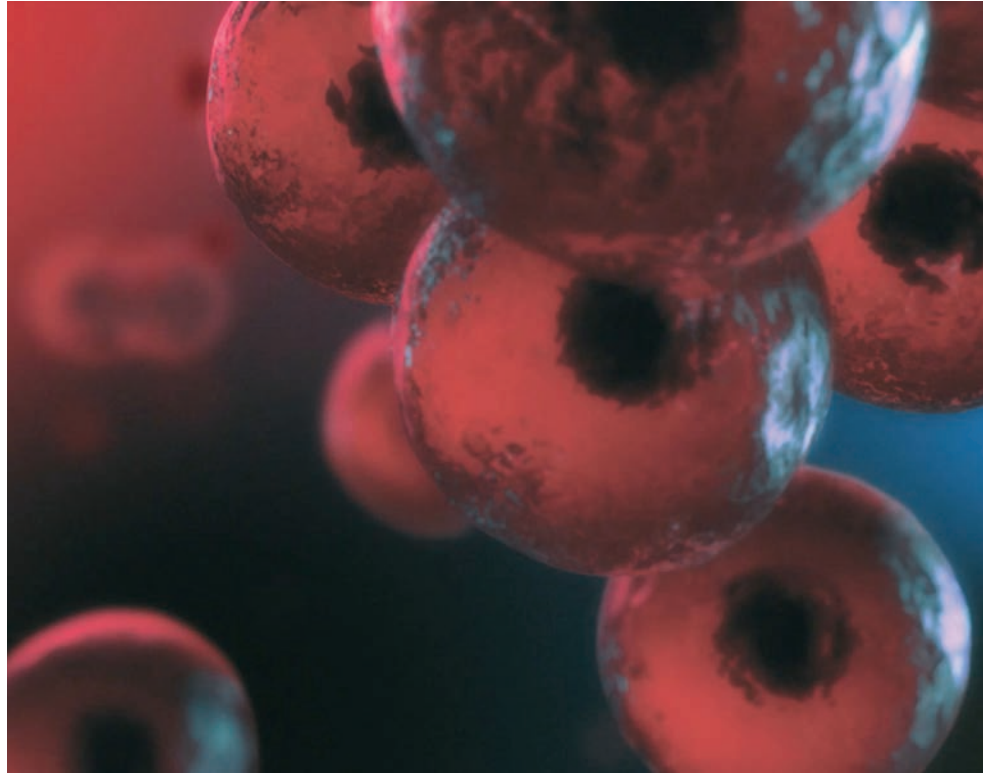
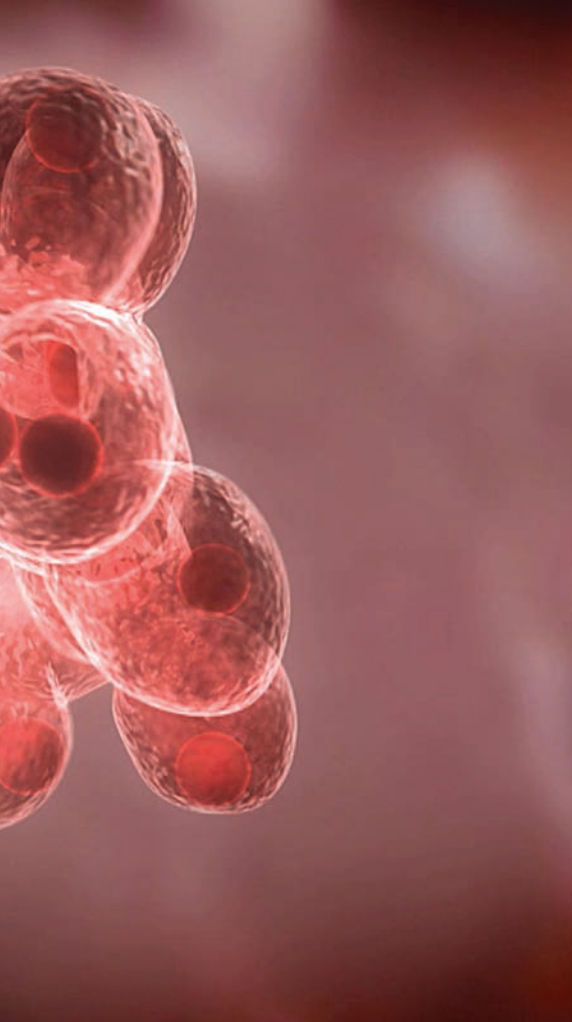


overcoming batch-to-batch variations, and developing specialized media for diverse cell types or applications.

Innovations

Many current innovations focus on serum-free, chemically defined media for various cell types, incorporating components that mimic in vivo environments. Advancements include using advanced analytics, machine learning, and bioprocess engineering

Credit: Corning Life Sciences



to develop superior media formulations, improving scalability, and performance. Some drug developers are also shifting from traditional monolayer cell cultures to 3D cell cultures that allow cells to grow in a more physiologically relevant environment that resembles tissue structures. 3D culture offers improved

cell-cell interactions and mimics in vivo conditions better for studying complex cell behaviors, drug responses, and disease modeling.

Some companies may seek custom media for unique cell types, either when existing formulations fail to meet precise growth requirements or for logistical reasons related to efficient scaling up. Tailored media can help enhance cell viability, productivity, and functionality, which are crucial for research or production processes.

The future

The future of cell culture media involves personalized formulations tailored for specific cellular functions or disease models. Advancements in bioengineering, microfluidics, and organoid technologies may shape media design, allowing more accurate replication of in vivo conditions and enabling precise control over cell behavior and function. Additionally, sustainable, animal-free media could become more commonly used to meet ethical and regulatory demands.

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Core Topic
**Small Molecule
Manufacture**

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Oligo engineering. Alltrna has presented data showing how it has applied machine learning to engineer transfer RNA (tRNA) oligonucleotides for two different premature termination codons prevalent in Stop Codon Disease. The platform was used to optimize sequences and modifications from natural tRNAs to increase activity by ~100 fold. CEO of Alltrna, Michelle Werner said in a statement: “The data demonstrate the power of Alltrna's platform to identify key combinations of tRNA sequences and modifications and precisely design tRNA oligonucleotides with significantly improved in vivo activity. With optimized engineered tRNAs for the two most prevalent premature termination codons, we are advancing preclinical studies for our first Stop Codon Disease indications.”

FDA under fire. The US House Committee on Oversight and Accountability has questioned FDA commissioner Robert Califf on “areas of concern” at the agency, including drug shortages and a failure to return to pre-pandemic levels of foreign inspections. The agency is accused of being unprepared for crises and failing to do “the bare minimum” in carrying out its core mission. Califf agreed that the agency needed to do more inspections, but also added that modernization of data systems was important to help target inspections.

Cyst study. The FDA has cleared the Investigational New Drug application for Vertex's autosomal dominant polycystic kidney disease treatment VX-407. The drug is a first-in-class small molecule corrector targeting patients with a genetic variant in a subset of PKD1, which leads to loss of PC1 function and results in cyst growth. Around 10 percent of patients with the disease have this variant. A phase I study commenced in March. CMO Carmen Bozic said, “Just as our approach in cystic fibrosis allowed us to reach more patients over time, our goal here is to serially innovate to reach the 250,000 people suffering from ADPKD.”

Semaglutide safety. Both the FDA and EMA have found no evidence of suicide or self harm as a result of consumption of Novo Nordisk's Wegovy (semaglutide) following an investigation beginning in July 2023. Three cases of potential suicidal risks were reported by the Iceland Medicines Agency, prompting the analysis of the ingredient semaglutide, which is also in Type II Diabetes drug Ozempic. The findings of a study published in January (DOI: 10.1038/s41591-023-02672-2) “do not support higher risks of suicidal ideation with semaglutide compared with non-GLP1R agonist anti-obesity or anti-diabetes medications.”

IN OTHER NEWS

Research team discovers method to deliver antisense oligonucleotides to targets inside cancer cells (DOI: 10.1093/nar/gkae245).

Novartis implements manufacturing adjustments for ribociclib to ensure alignment with latest regulatory standards in eBC.

University of Manchester researchers develop molecular device that controls the release of multiple small molecules using force (DOI: 10.1038/s41586-024-07154-0).

Pfizer agrees to settle in excess of 10,000 lawsuits claiming knowledge of carcinogens in heartburn treatment Zantac (ranitidine).

GSK reports positive results from phase III trial for gepotidacin, which has a novel mechanism of action in uncomplicated urogenital gonorrhoea.

The Start of a Journey

Meet Brad Hocking – a final year PhD student at Imperial College London who is passionate about small molecule drug discovery. Hocking is working under the joint supervision of David Mann and Alan Armstrong on projects in covalent fragment based drug discovery. Here, he discusses his work and what inspired his interest in this field.

What first inspired your interest in science?

At Imperial College London, I've been working with David Mann and Alan Armstrong on covalent fragment-based drug discovery projects – I'm finished in the lab (for now!), so by the time this reaches publication I may have submitted my thesis! From when I was quite young, I'd been curious about the natural world and how things worked, so science as a discipline drew me in because it offered answers and ways of investigating them for myself. Since my high school days, my interests have been split between the disciplines of chemistry and biology, so I studied natural sciences with my final two years specializing in synthetic organic chemistry for my undergraduate/MSci.

And what inspired your interest in drug discovery – particularly small molecule drug discovery?

Drug discovery as a field contributes toward improving the future of healthcare and improving people's length and quality of life, which gives working in the field a good sense of purpose. From the scientific side, I think



the practicality of small molecules is that the science is quite well-established, the field is fruitful, and we have a lot of prior blueprints of how to achieve success. The other draw is the creativity that our wealth of synthetic chemistry methodology enables – there's a huge accessible chemical space available to exploit to really tailor and perfect a molecule's structure and properties for our purposes. Then there's the covalent aspect, which adds reactivity to the molecules for extended target engagement and allows us to hit some hard targets, but also comes with its own set of challenges.

Tell us about your work with covalent drug discovery...

My project is funded by the charity Sarcoma UK, and we are taking on a challenging oncology target associated with poor prognosis in several sarcoma subtypes. Sarcomas are typically fast-growing bone and soft tissue cancers with diverse origins. They are very

heterogeneous within and across disease subtypes. This means there aren't a lot of targeted therapies available that are applicable across a range of sarcoma subtypes. There are a few proteins without approved drugs that we can try to target for maximum impact across sarcoma subtypes – of which my target is one. On the project, I've been using techniques ranging from fragment screening assays, protein mass spectrometry, protein crystallography and synthetic chemistry.

What have been the most exciting moments of the research so far?

The most exciting moment would have to be when I diffracted one of my most recent protein-fragment adduct crystals at a much higher resolution (1.4 Å) than my previous structures. This was exciting because of how challenging every step of the way is, from obtaining useful protein crystals to correctly cryoprotecting and harvesting them, then getting useful data out of them on the beamline. When I loaded



the exciting crystal in question I had high hopes for it (on the beamline camera it was much bigger than the others). When I performed a small screening diffraction, the diffraction images were immediately beautiful, and I knew it was going to be a good quality dataset.

And what have been the biggest challenges?

Less related to technical challenges – but the COVID-19 pandemic couldn't have happened at a more inconvenient time for me. I started my PhD in February 2020 after a brief break post-MSci. Within a couple of months, I was back out of the lab due to lockdowns. Even after lockdowns there were strict COVID-19 restrictions in place and late shift work patterns.

In addition, learning and applying biochemistry techniques which I had nearly no experience of during this time was particularly challenging!

What analytical equipment has been involved in your work?

I've performed most routine 1D and 2D small molecule NMR analysis and IR analysis in synthetic portions of my work, but working in the field of protein modifications means that intact protein LC-MS has been the primary analytical technique I've used. I set this up for our group at the Agilent Measurement Suite (AMS) in the Imperial College Molecular Sciences Research Hub (MSRH). I've primarily been using an Agilent 6545 Advancebio LC/QTOF set up in the suite – I bring my own C4 column, samples, and solutions to run the instrument. Separately from the AMS, I've also had the chance to use a RapidFire high throughput LC system, which is a very cool piece of kit those working in covalent drug discovery are probably aware of or familiar with! They take multi-well plates and can get to throughputs of 3 samples per

minute with online desalting for protein screening workflows. It can run a 384 well plate in about 2 hours or so.

It's really important for researchers to have access to good equipment. Researchers want good data, quickly and without having to navigate unreliable or temperamental instrumentation or unnecessarily complex software. It also saves time and cost for funders and means projects can move much faster. The best systems offer those things – accuracy, reproducibility, reliability, throughput – to make the most of research time. The most frustrating experiences come when a costly and fiddly experiment is spoiled or slowed down by broken or inaccurate instrumentation. Another important factor is product aftercare and servicing provided by companies, which can make or break an experience using even the best equipment.

Is it easy for people to use these techniques without analytical skills?

Between my chemistry background and investing in developing my analytical skills and knowledge, things have likely been a lot easier than if I had no analytical skills. If good protocols have been set up, and providing everything works correctly, somebody without any analytical skills could load samples and follow a workflow using any well-designed software to get their data without any issues. But for anything beyond that, it's important to have a solid understanding of the instrument, method and data being generated to ensure the experiments are rigorous and the data generated is good quality.

Are you considering working in the pharma industry after your studies?

I'm currently applying for grants to continue my current work as a postdoc for a short while. After that, it depends! To try to answer the classic academia versus industry question, I don't feel too strongly either way, so it will come down

"I've been using techniques ranging from fragment screening assays, protein mass spectrometry, protein crystallography and synthetic chemistry."

to opportunities and where they lie. I do really enjoy teaching and mentoring students in the academic environment, but longer term I think the pharma industry is most likely for me. The pharma industry is well-resourced and tends to have better progression opportunities than academia for primarily lab-based scientists, so I think industry would best suit my life and career goals.

I enjoy working in drug discovery so I would like to stay in this field, and I really enjoy working in the lab day-to-day, so I would hopefully stay lab-based for quite a while longer. I've also been considering moving abroad for a stint. My longer-term career goal is to work towards being a project lead or PI and use my interdisciplinary training to tie together broad ranging projects.

Brad Hocking would like to thank Sarcoma UK for funding his work. Sarcoma UK fund research, educate healthcare providers, and provide an important network of support for everyone affected by sarcoma – patients, families and caregivers.

Keep Your Eye on the Supply

**Best
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*Technology
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Compliance*

Almost a quarter of the way through the 21st century, it is hard to believe – and even harder to accept – that the deaths of children can be attributed to cough medicines manufactured with substandard excipients. IPEC Federation is clear: all stakeholders must not suffer complacency when it comes to supply chains.

By Stephanie Vine, Editor

In January 2023, the World Health Organization (WHO) issued an urgent call about the dangers of contaminated cough medicines, following the deaths of children in Gambia, Indonesia, and other countries. Certain cough medicines were found to contain diethylene glycol (DEG) or ethylene glycol (EG) – both of which are toxic to humans. WHO does not believe these are isolated incidents and has called for “key stakeholders engaged in the medical supply chain to take immediate and coordinated action.”

For regulators and governments, this call to action means detecting and removing substandard products from circulation, assigning resources for risk-based inspections of pharmaceutical manufacturers, increasing market surveillance, and taking any necessary enforcement action. For medicine makers, it means purchasing pharmaceutical grade excipients from qualified suppliers, including distributors, conducting testing, providing assurance of quality, and keeping records to facilitate supply chain traceability. Suppliers also have a role to play in checking for evidence of falsification, keeping correct records, and ensuring they only sell or distribute products to approved sources.

Incidents of DEG poisoning are not new. The first incident was reported in 1937 in the US, when a company in Tennessee manufactured sulfanilamide dissolved with DEG. Various other cases have emerged over the years, with a spate of deaths in the 1990s leading industry stakeholders – such as WHO and IPEC – to develop guideline documents helping to ensure the security of the supply chain and protecting patients.

In light of recent incidents, IPEC Federation says it will revisit and update its guidelines. Here, we speak with Frank Milek, former President of the association who has remained involved in IPEC for more than 25 years.

How did the IPEC Federation get involved with supply chain security for excipients?

WHO got involved in the question of supply chain security of excipients in the 1990s after a high-profile incident in Haiti involving DEG-contaminated glycerol; IPEC also got involved at this time. Back then, there was no IPEC Federation, but there were three regional IPECs: IPEC-Americas, IPEC Europe, and IPEC Japan. WHO’s headquarters are in Geneva, so IPEC Europe was the


main point of contact and represented all three IPECs. We were asked by WHO to give our opinions on the root cause of the incident and to provide suggestions. IPEC Europe identified the need for a focus on the supply chain of excipients, particularly given their high diversity.

What led the IPEC Federation to update its position paper on supply chain security for excipients?

“IPEC Europe identified the need for a focus on the supply chain of excipients, particularly given their high diversity.”

Examples of Tragedy


Haiti: 1995–1996



In Haiti from November 1995 to June 1996, 86 children were diagnosed with acute anuric renal failure. Most did not survive. A report found that DEG-contaminated glycerin, imported from another country, had been used to manufacture acetaminophen syrups, which the children had consumed.


CDC, “Fatalities Associated with Ingestion of Diethylene Glycol-Contaminated Glycerin Used to Manufacture Acetaminophen Syrup – Haiti, November 1995–June 1996,” (1996).

Panama: 2007



In 2006, a physician in Panama noted a number of patients with unexplained acute renal failure. The cause was later found to be cough syrups contaminated with diethylene glycol. At least 100 people died, but some claim that the number could be significantly higher. Glycerine used to produce the syrup had reportedly been labelled as 99.5 percent pure and had arrived in Panama via a network of distributors. Over the course of the supply chain, the glycerine was not tested, and the certificate of authenticity was altered. The glycerine was found to have originated from China, where it was originally labelled as “TD glycerine.” Nobody questioned what this meant at the time, but it is believed to stand for “tidai” which means “substitute.”

A number of individuals were sent to prison in Panama in 2016. *The New York Times* (2007).



In 2003, WHO published the Good Trade and Distribution Practices for Pharmaceutical Starting Materials, and in 2006, IPEC-Americas and IPEC Europe jointly published the Good Distribution Guide for Pharmaceutical Excipients (later revised and re-published by the IPEC Federation in 2017), which was the outcome of the collaboration with WHO. The Guide was intended

to help all stakeholders in the global supply chain for pharmaceutical excipients to improve safety and avoid contamination cases. Guidelines are not the same as regulations, so we also developed a position paper to explain why we thought it was important to use the guide.

After we published the guidelines and position paper, the number of incidents

Points for Consideration

The IPEC Federation position paper states that pharma manufacturers should consider the following:

Awareness and robust application of guides, standards and regulatory requirements

Starting materials to be purchased from qualified and approved suppliers

Purchase of ingredients suitable for use in pharmaceutical products/ pharmaceutical grade excipients, no use of industrial grade chemicals as pharmaceutical excipients
Robust incoming goods inspection,

quality control testing and product release according to applicable monographs or equivalent validated and appropriate internal method(s)

Full traceability of the supply chain back to the original excipient manufacturer

Awareness and application of Risk Management principles

Training system and records

Additional excerpts:

“Initial findings from WHO indicate the following areas require more focus and in-depth investigation:

- Criminal activity
- Falsification of records (namely

Certificates of Analysis)

- Supply Chain complexity
- Lack of or insufficient QC testing
- Use of industrial grade material”

“IPEC Federation wishes to reemphasize the points made in the Introduction that ethylene glycol and diethylene glycol are chemicals for use in industrial applications only, such as for example, industrial solvents, coolants and antifreeze agents. Ethylene glycol and diethylene glycol are not approved for use in pharmaceutical applications. When consumed by human beings, especially young children, e.g., as components of a medicinal syrup or other liquid pharmaceutical formulations, they lead to significant toxicity effects. Depending on the dose, these effects may include severe kidney damage potentially resulting in death.”

caused by DEG contamination seemed to come down for 10 years. Recently, however, cases have started to appear again – and we can see that the root causes of today’s cases are likely similar to the earlier cases. We engaged with WHO to discuss the situation and what support we can offer. From these discussions, we decided to update our position paper to reinforce our opinion on how to safely manage excipient supply chains.

Why do you think incidents caused by DEG contamination are again on the rise?

We believe that the good practices published in the past – and the publicity around these guidelines – have helped to prevent substandard medicines caused by substandard ingredients. Yet, it’s clear that these good practices are not

always implemented properly by all companies. Perhaps some stakeholders are becoming more lenient or less cautious. We cannot say for sure why these cases are increasing – especially when the investigators in many of the cases do not always disclose details about exactly how the contamination occurred. However, we have observed that many of the cases come from environments where drugs are under price pressure, or in lower income countries where there is less regulatory oversight. In environments with less regulatory resources and scrutiny over supply chains, there are more opportunities for quality standards to be jeopardized, whether through criminal intent or lack of knowledge of best practices.

The FDA has released new guidance for industry in response to the

“We must all remain vigilant – and know that global supply chains carry risks.”

situation. How would you compare the FDA’s approach with that of WHO in terms of addressing the root cause of the incidents?

Both approaches make sense and, in combination, will help to improve the situation. It is always better to heal the problem at its root cause. WHO is still investigating the causes of recent



incidents, but from there stakeholders can consider actions to systematically improve processes. With more incidents occurring, it is more important than ever before for stakeholders in the affected countries – including excipient manufacturers, finished dosage form manufacturers, wholesalers and drug sellers, and regulators – to come together and be made aware of the problems. They must know that, to resolve them, they must apply best practices and every single principle of a standard across the entire supply chain. It's not enough to just test at the end of the supply chain to ensure quality because you can only test if you know what you are testing for. There are many opportunities in the supply chain to spoil the quality of the product, and if you don't have the right test strategy in place, you will fail to identify the problems.

In May 2023, the FDA published guidance for industry focusing on the quality control approach and to ensure that excipients – particularly excipients at high risk of DEG contamination – are tested by pharmaceutical companies. At the IPEC Federation, we believe that this should not be the only approach. Using this approach alone will not avoid future incidents. We need both a quality control approach and good distribution practices for pharmaceutical excipients.

When bringing stakeholders together, we also must do better in making arguments to convince people that they must ensure they are doing their duties at every point in the supply chain. It is not enough to agree with a supplier on the specification and basic quality of an excipient, and to receive and test that excipient before use. You must understand the supply chain. Who is involved? Who is handling the product and storing the product? What about repackaging? You must understand all of this so that you can manage the risk.

What action(s) is the IPEC Federation planning in response to the situation? We must all remain vigilant – and know that global supply chains carry risks. Supply chains today are far more complex than in the past, and the more steps there are in a supply chain, the greater the risks of companies or individuals being able to slip in substandard materials. IPEC Federation is working on the revision of our Good Distribution Practices guideline – with publication planned for 2024. Our revised guidelines will take into account the conclusions that WHO draws from its investigations account. We are also open to cooperating with WHO if they want to involve us in their activities to improve the situation.

The Gambia Investigation



According to a report from the US Centers for Disease Control and Prevention, DEG-contaminated medicines are a particular threat to low income countries: “Inadequate regulatory structures make the sale of medications from international markets an especially high-risk activity in low-resource settings.”

The report was produced in response to DEG-contaminated medicines in the Gambia and stated: “A large cluster of acute kidney injury cases affecting children in The Gambia in 2022 was associated with case fatality rates >80%. The implicated syrup-based pediatric medications that had been administered to patients were imported from a single Indian manufacturer. This is one of the first documented DEG outbreaks in which contaminated medications were imported rather than being domestically manufactured.

“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.”

CDC, “Acute Kidney Injury Among Children Likely Associated with Diethylene Glycol–Contaminated Medications — The Gambia, June–September 2022,” (2023).

A Mission Focused on Quality and Safety

Following on from deaths attributed to contaminated cough medicines, here's how the US Pharmacopeia (USP) is helping promote testing for DEG and EG

By Chaitanya Koduri, Director, International Government and Regulatory Engagement at the US Pharmacopeia

Diethylene glycol (DEG) and ethylene glycol (EG) are toxic when ingested above acceptable limits. They can make their way into drug products as process impurities during the manufacture of four sugar alcohols (for example, sorbitol and maltitol solutions) and excipients manufactured with ethylene oxide as a starting material (for example, polyethylene glycol). Process-related impurities, such as EG, DEG (a dimer of EG), and triethylene glycol (TEG; a trimer of EG), may arise from the hydrogenation process of sugar alcohols or the reaction of ethylene oxide with water.

DEG and EG can also appear in drug products through economically motivated adulteration of high-risk excipients, such as glycerin and propylene glycol, which have a similar taste and appearance but are less expensive. Excipients can comprise up to 90 percent of a drug formulation, but their quality is often overlooked.

DEG and EG can find their way into the supply chain of any country. For products entering the US, testing of raw materials, active pharmaceutical ingredients, and inactive ingredients by the drug manufacturer is a cGMP requirement. However, low-to-middle-income countries may not have the same quality assurance requirements and/or resources to be able to identify deadly contaminants in medicines.

Key factors contributing to the contamination of final drug products

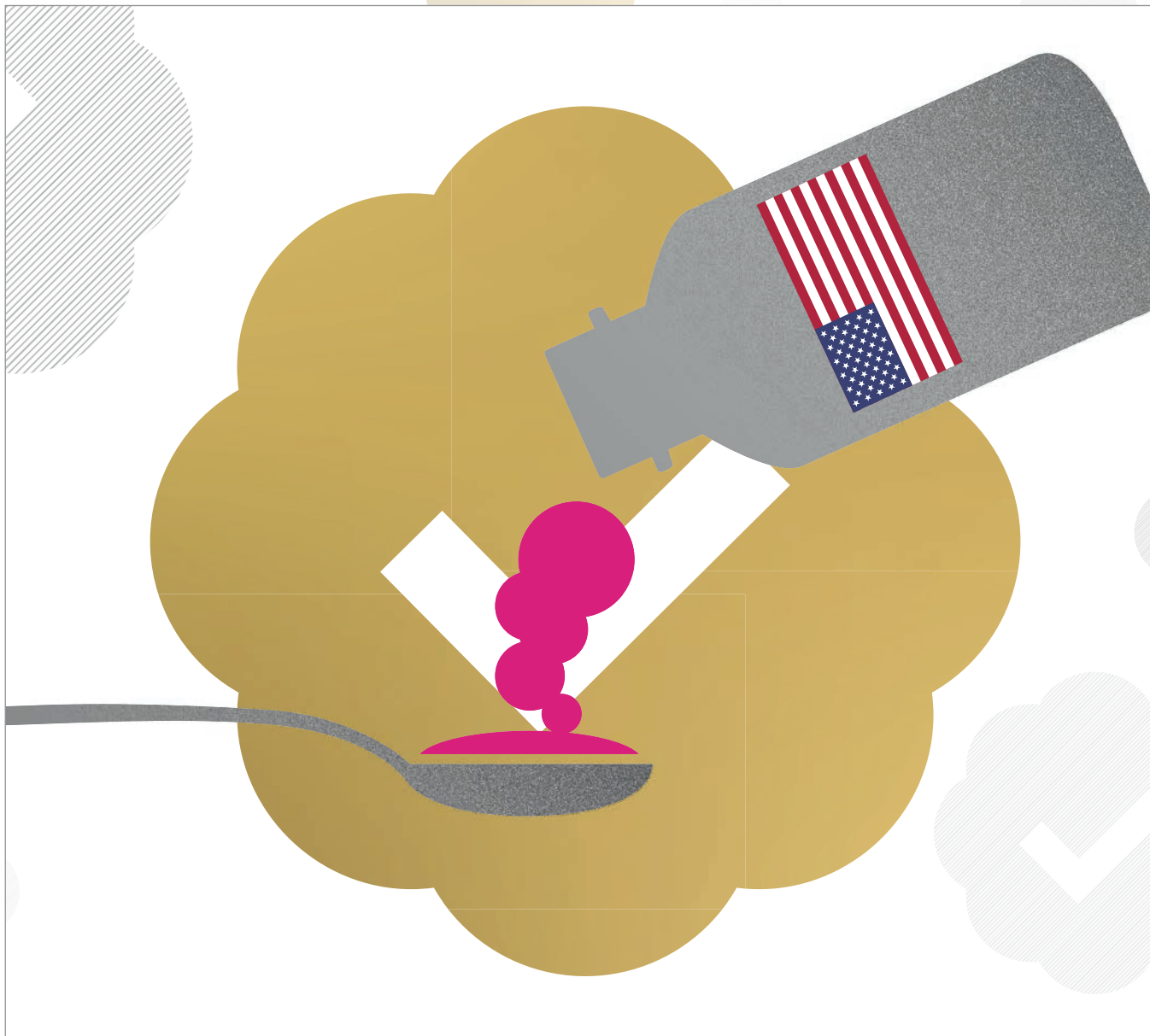
with DEG or EG include inadequate supplier qualification (lack of origin), lack of appropriate identity testing, and a complex supply chain (chain of custody). More about this is written on USP's website: "Ensuring Product Safety: U.S. FDA Guidance on Testing High-Risk Drug Components for Diethylene Glycol and Ethylene Glycol."

DEG and EG adulteration and contamination have always been a serious public health concern, with deaths and adverse health outcomes caused by DEG and EG contamination occurring as early as 1937. The deaths of children have also been reported in many geographies over the last several decades. In 2022 and 2023, more than 300 deaths were reported because of people consuming liquid drug products contaminated with DEG and EG, including cough syrups and analgesics. Indeed, the seriousness of the issue has gained international attention in the past two years because of reports from multiple countries of patient deaths and illnesses, including young children.

Cough syrup and cold medicines are particularly vulnerable to adulteration because of cost pressure and commoditization. In many of the cases of DEG and EG contaminations seen with cough syrups, one of the main ingredients, glycerin, was replaced by

DEG, which is cheaper. The physical properties of DEG and EG as colorless and sweet liquids make them difficult for patients, caregivers, or physicians

"DEG and EG adulteration and contamination have always been a serious public health concern, with deaths and adverse health outcomes caused by DEG and EG contamination occurring as early as 1937."



to detect without laboratory testing, making these formulations more susceptible to contamination.

We have also seen an increase in the number of US FDA warning letters sent to manufacturers regarding DEG and EG testing over the past year. For context, there have been more than 40 warning letters from the US FDA on

this topic since 2019 – but 33 of those have been issued since the start of 2023. These letters were sent to manufacturers that did not test or inadequately tested drug components for the presence of DEG or EG.

Testing requirements

US regulations require testing for

impurities and adulterants in all raw materials used in medicines. Because of the high risk involved in DEG and EG contaminations, the US FDA Center for Drug Evaluation and Research issued additional guidance for industry members in May 2023 titled “Testing of Glycerin, Propylene Glycol, Maltitol Solution, Hydrogenated Starch Hydrolysate,

Sorbitol Solution, and Other High-Risk Drug Components for Diethylene Glycol and Ethylene Glycol.”

If a manufacturer fails to follow this guidance, it can result in an FDA warning letter, import alert, and product recall, which is not only expensive, but also tarnishes the recipient organization’s reputation.

The latest FDA guidance is an update to the 2007 guidance on DEG. It identifies not only DEG but also EG as potential contaminants in high-risk components, including those listed in the title. It requires compliance with the identity standards for a drug, including drug components, with a name recognized in the USP-NF. The USP has several standards, including monographs, documentary standards, and reference standards, for several of the high-risk drug components – and has also organized multiple training workshops for manufacturers to increase their understanding of the use of standards for the quality assurance of excipients.

The guidance also states the incidents in liquid drug products before 2020 resulted because drug product manufacturers:

- Did not perform full identity testing on the glycerin raw material, including tests to quantify the amount of DEG present and to verify the purity of glycerin.
- Relied on the certificates of analysis provided by the supplier of the glycerin.
- Had limited information on the entire supply chain and chain of custody of the glycerin raw material, as it was not noted on the certificates of analysis.

Pharmacopeial standards are science-based, data-driven, validated, and characterized, and they exist to confirm the identity, purity, strength, and quality of various drug components in drug

development and manufacturing. These standards are used by manufacturers to prevent quality issues. The FDA requires that the identity of each component in a drug is verified, and that each component be tested for conformity with all appropriate written specifications for purity, strength, and quality. In place of such testing by the manufacturer, an analysis report may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such components by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier’s analyses through appropriate validation of the supplier’s test results at appropriate intervals.

The new FDA guidance from 2023 reinforces the requirement of identity testing and outlines recommendations for drug product manufacturers, repackers, preparers, and distributors of high-risk drug components, and for pharmacies. The following recommendations have been underscored:

1. Drug product manufacturers must perform identity tests on samples from all containers of all lots of high-risk drug components.
2. For high-risk drug components, where the DEG and EG tests are not included in the identification test of the USP-NF monograph, a manufacturer uses a suitable and equivalent procedure that includes a test to detect and quantify DEG and EG, with a recommended safety limit of no more than 0.10 percent*.
3. Repackers, preparers, and distributors of high-risk components for use in drug products must test the high-risk components that are used, sold for use, or intended for use in drug products, providing the details of the original manufacturer in the certificates of analysis of each lot.

“Given the events surrounding substandard and falsified medicines that occurred in 2022 and 2023, it is clear that stakeholders must think differently about excipient quality.”

To prevent DEG and EG contaminations, manufacturers must test each incoming shipment (ideally each container of each shipment) of the high-risk excipient to ensure that levels of DEG and EG meet the limit set in the applicable pharmacopeia or regulatory guidance, have full transparency of the supply chain of the excipient, and purchase from a supplier – qualified by the manufacturer – that follows cGMP. In the absence of a pharmacopeial specification or regulatory guidance, they must verify that an excipient is safe in the amount it will be used.

Excipient manufacturers also make the same chemicals for use in non-pharmaceutical products in much larger volumes due to demand for that type of use. It is crucial that drug companies ensure that the excipients they receive have been manufactured according to applicable cGMP and are suitable for use in medicines.

Ensuring safety

At the USP, our mission is to ensure access to quality medicines and improve global health through public standards. Incidents such as contamination from DEG and EG reinforce the need for standards and the importance of investments in continuing to advocate for regulations that prioritize testing the quality of raw materials and industry practices that ensure patient safety.

Given the events surrounding substandard and falsified medicines that occurred in 2022 and 2023, it is clear that stakeholders must think differently about excipient quality. Monitoring, controlling, and testing the quality of all excipients in the medicines supply chain is necessary to protect patient safety.

As part of our work, we want to support all those involved in the global medicine manufacturing supply chain, which is why we have developed documentary standards that provide validated test procedures to establish the identity, purity, and quality of excipients through the USP–National Formulary (USP-NF); USP Reference Standards for excipients that have been tested and approved as suitable for use as comparison standards in USP-NF tests and assays; Ingredient Verification programs to test products, check documentation, and audit API, excipient, and dietary ingredients manufacturers; and on-demand learning opportunities through USP Education.

USP has also developed a free toolkit for DEG and EG in response to the World Health Organization issuing a call to action about substandard medicines containing unsafe amounts of these contaminants. The toolkit is designed to be used by manufacturers, regulators, and country pharmacopeias as a solution to address contaminations associated with allergy, cold, and cough medicines. It includes all relevant chapters, monographs, and other resources needed to advocate for excipient quality

throughout the medicine supply chain – especially with high-risk components. Visit [USP.org](https://usp.org) to download the toolkit.

It is important for industry members to identify all their high-risk components and have a proactive risk mitigation plan in place. To increase awareness on mitigating issues with raw materials, there was a session at the 2023 Asia-Pacific Economic Cooperation (APEC) forum's Medical Product Supply Chain Dialogue titled "Mitigating and Managing Risks in Excipient Quality." The forum panel emphasized the importance of implementing crucial measures, such as excipient testing, supplier qualification, and risk management through harmonized standards and regulations. As part of the USP's APEC Center of Excellence status, we host the APEC Supply Chain Security Toolkit, which serves as a global resource to establish effective training programs, best practices, and processes for securing the global supply chain of medical products.

The FDA is also taking action to mitigate DEG and EG contaminations. Its May 2023 guidance requires compliance with the identity standards for a drug with a name recognized with the USP-NF, including drug components. Regulatory agencies in different countries can use this guidance, in addition to the World Health Organization (WHO) draft of a working document on cGMP for excipients used in pharmaceutical manufacturing, among other resources from regulatory agencies. USP is also working closely with FDA on the update of the documentary standard for polyethylene glycol (PEG). USP plans to revise the existing PEG monograph shortly and potentially propose several available DEG and EG testing methods through another avenue.

To ensure the safety of excipients, pharmaceutical manufacturers can work to increase transparency surrounding the origin of excipients, incorporate more testing throughout the supply chain, and

verify the supplier's certificate of analysis by conducting their own testing of incoming excipients. Users can find more information from USP Chapter <1080> Bulk Pharmaceutical Excipients—Certificate of Analysis in our toolkit.

Increasing education efforts can also ensure the safety of excipients. Sometimes there is a lack of awareness about needing a special grade for pharmaceutical use, which can result in the excipient manufacturer using the wrong grade excipient in a drug product. This single mistake can affect a drug product's manufacturing or performance and can also possibly endanger patients who use the product.

Unfortunately, DEG and EG adulteration and contaminations are not the only examples of how poor-quality excipients can lead to patient harm. By following pharmacopeial standards and testing every drug component before use, manufacturers can help protect public health by preventing contaminated and/or ineffective medicines from entering the supply chain. Excipient quality is critical to the integrity and functionality of a medicine and it cannot be an afterthought.

** The USP-NF monograph on Polyethylene glycol (PEG) has a test for DEG and EG in the impurities section. The US FDA sent USP a letter requesting that the DEG and EG test be included in the Identification section of the PEG monograph for PEG above molecular weight of 1000. The USP Excipients Expert Committee is revisiting these two methods to determine if they are still relevant and if a test for molecular weights over 1000 should be developed based on newer technology. We are in the process of discussing with the FDA to get clarification for monographs that may have different specifications. Since the FDA did not submit a request to the USP to change the acceptance criteria, at this point, the compendial specifications for PEG are still what is listed in the monograph "NMT 0.25% of the sum of ethylene glycol and diethylene glycol" or "The absorbance of the Sample solution does not exceed that of the Standard solution, corresponding to NMT 0.25% of combined ethylene glycol and diethylene glycol" depending on the molecular weight.*

The Clinical Cosmos

**NextGen***R&D pipeline
New technology
Future trends*

The exploration and exploitation of the unique environment of space and its implications for clinical research

By Deepika Khedekar, Associate Centralized Clinical Trial Lead at IQVIA

Vast and enigmatic, space has always been the focus of human obsession. It also offers a unique environment – a “hotspot”, if you will – for researchers. Space research not only helps us broaden our understanding of the cosmos, it lays the groundwork for a deeper examination of the challenges faced in Earth-based research. For example, Earth's gravitational forces impact cellular behaviors and interactions, making it challenging to study cells in their true three-dimensional context. There are many ways in which space could be a promising avenue for more accurate and accelerated research.

Microgravity: a new frontier for laboratories

In microgravity, cells experience minimal gravitational forces. They can grow in three-dimensional structures in a way that mimics their natural state within the human body, facilitating more precise observations, particularly in understanding cellular interactions, growth dynamics, and treatment responses. A notable example is the growth of protein crystals, which were found to be larger and less flawed than those grown on Earth, offering deeper insights into their structure and functions.

The absence of gravity brings about significant alterations in well-known physical phenomena. The settling of

heavier particles – sedimentation – becomes negligible, as does convection, the movement of molecules driven by temperature differences. In contrast, diffusion, the movement of molecules from high to low concentration, becomes the dominant force in the microgravity environment of space. This shift has profound implications for cellular biochemistry. Cells adapted to Earth's gravitational pull may function differently, affecting processes such as nutrient absorption and waste expulsion. Recognizing these changes, the pharmaceutical industry is now exploring how space-based molecular interactions can pave the way for enhanced drug development on our planet, and new perspectives on areas such as drug interactions and stability.

Off the top of my head, I can offer a couple of examples of organizations embracing off-planet research. First, Budapest-based space chemistry research corporation InnoStudio has conducted experiments on the International Space Station (ISS) to determine if microgravity could enhance the stability of remdesivir and broaden its applications by reducing the risk profile (1). The company is also looking at other novel APIs and how they behave in microgravity. Second (and going back to protein crystallization in

space), Merck, Sharp & Dohme has been investigating crystallization processes for biologics with a view to simplifying drug delivery (2). The study of proteins could help us to understand various health conditions and prompt investigations into other pharmaceutical relevant areas, such as the effects of microgravity on our immune system. And back on Earth, a coordinated effort led by the University of Barcelona sought to simulate microgravity conditions using parabolic flights to discern the impact of this environment on our immune defenses (3). Preliminary findings suggest that microgravity might not significantly compromise our immune system – at least not during short exposures (4). This research not only has implications for future space missions, but also provides invaluable insights for space tourism and potential long-term human habitation in space.

As we delve deeper into the effects of space on our physiology, the heart emerges as another critical area of study. NASA's experiments have revealed that microgravity can be beneficial for stem cells and their remarkable ability to develop into various specialized cell types. In this context, stem cells in space have shown to grow into a type of heart muscle cells known as cardiomyocytes – the cells responsible for the contraction of the heart,

allowing it to pump blood effectively. One specific study, known as the MVP Cell-03 study (5), demonstrated that microgravity can boost the production of cardiomyocytes. These findings are not just academic; they have real-world implications. Such revelations could lead to innovative treatments for cardiac abnormalities, both those induced by spaceflight and those prevalent on Earth.

Similarly, space-based clinical research is shining a light on one of the most formidable health challenges we face here on Earth: cancer.

Every year, cancer claims 10 million lives, a number surpassing the total population of Switzerland. Could the unique conditions of microgravity provide fresh insights? A UK-based research initiative is exploring the three-dimensional growth and spread of cancer cells in the microgravity environment of the ISS (6). The weightlessness of space allows cancer cells to form tumor spheroids or organoids that closely resemble genuine growth patterns in the human body, providing researchers with a unique opportunity to examine cancer cell behavior, evolution, spread, and reactions to different treatments. In particular, this research team is interested in diffuse midline glioma, a devastating childhood cancer known for affecting critical areas of the brain and spinal cord, making it particularly challenging to treat. Children diagnosed with diffuse midline gliomas often die within a year after their initial diagnosis, and there are no effective treatments.

The insights gleaned from these space-based studies hold the potential to revolutionize our approach to cancer and other diseases.

The challenges in space
Conducting experiments in space requires intricate planning, coordination, and execution. The process of sending equipment and samples to and from is both time-consuming

and expensive. In many cases, space-based research is inaccessible for smaller research entities. Moreover, the unique variables introduced by the microgravity environment can complicate the interpretation of experimental results. Other factors, such as increased radiation exposure, may also influence experimental outcomes, necessitating additional controls and considerations. Collaborations with private space companies can provide additional resources, expertise, and capabilities, but other solutions are also being developed.

Advanced robotics, for example, could eventually streamline the process of transporting and handling clinical samples, reduce human error, and increase efficiency. Robotic arms, such as the Canadarm2 (8) have already been instrumental in capturing cargo spacecraft and assisting with experiments aboard the ISS. Telemedicine and remote monitoring technologies can help manage physiological changes in astronauts, with wearable health monitors already being used to track astronauts' vitals in real-time and send data back to Earth for analysis (9).

Advanced shielding technologies could also mitigate the effects of increased radiation exposure in space, providing a more controlled environment for these clinical research experiments. NASA's development of radiation shielding materials, for instance, can protect both equipment and astronauts from harmful cosmic rays.


Beyond the technical and logistical challenges, another key question is: do we have a governance compass in place to balance research opportunities with the myriad of ethical, legal, and safety implications unique to the interstellar domain? As space emerges as a promising domain for clinical research, the imperative for a comprehensive

governance framework becomes evident. The unforgiving nature of space demands rigorous safety protocols, so precautions must be in place to shield researchers and participants – and to handle emergencies.

Data collection in space presents its own set of challenges, given the constraints on tools and technologies. How can we vouch for the accuracy and reliability of this data, and what measures are in place to ensure seamless data transmission to Earth? A comprehensive governance framework for space-based clinical research is imperative to address the multifaceted challenges this frontier presents. It should account for the unique physiological responses in microgravity, establishing guidelines that ensure research findings are both relevant and applicable across environments. Safety protocols must be rigorous. Collaborative efforts between nations, space agencies, private entities, and the scientific community will be crucial in establishing guidelines that promote clinical innovation while safeguarding the integrity of space and its explorers.

Space, once the final frontier, could be a pivotal platform for research and innovation in the future, but with the human body responding differently in space's microgravity, there can be questions about whether the findings are universally applicable or space-specific. Are we truly maximizing the cosmic potential to reshape the future of healthcare, or merely echoing terrestrial pursuits in the cosmic arena? There is potential for conducting research in space, and it is an exciting field, but we should proceed with caution and ensure the research is conducted to a high standard – and with attention paid to ethics and responsibility.

References available online
<https://bit.ly/4bDH6ax>

A portrait of Anne Marie de Jonge-Schuermans, a woman with blonde hair, wearing a dark blazer and a patterned scarf. She is smiling slightly and looking towards the camera. The background is a colorful, abstract painting with blue, yellow, and orange strokes.

From Start-Up Biotech to the Boardroom

Sitting Down With...
Anne Marie de Jonge-Schuermans,
Board Member of the Swiss
Biotech Association and Global
Head of Biologics & Injectables
Operations at Sandoz

What is it about your current role that you love?

My career has progressed in unpredictable ways. I've worked in prescription pharma, OTC medicines, innovator biotech, and now I'm focused on biosimilars and generics, which I find very rewarding. You may know that Sandoz pioneered the launch of the world's first biosimilar in 2006. The drive for me is enabling more patients to access medicines by doing things smarter and more efficiently, so that we can offer the same products at more affordable prices.

I manage a couple of factories and the company has made substantial investments to ensure the future of our biosimilar business. We have 10 biosimilars on the market, and 24 biosimilars in our pipeline. We continuously scout the reference medicines market to select suitable candidates for biosimilars that we can develop and offer to patients at affordable prices. It's not easy to make a biosimilar, especially when you want to be the first to market, and there is always a lot of pressure to do it better, and faster – but that's also fun and rewarding too.

How did you come to work with the Swiss Biotech Association?

I previously worked for Sobi (Swedish Orphan Biovitrum), which acquired various small biotech companies. I became very interested in start-ups, followed some courses, and began doing some start-up coaching and advisory work. Through networking, I met Michael Altdorfer, CEO of the Swiss Biotech Association. The association is all about networking, sharing knowledge, and helping biotech companies be stronger together. I really liked the spirit of the association, so I was super happy when they asked me to join their board last year. Both small companies and big companies are members, and it has a very nice culture of connection and community. As an example of some of the work the association does, in January there

was a startup CEO day, which enabled CEOs to get together and share notes. How did you get funding? How do you manage recruitment? Which CRO did you work with? What kind of labs do you have? These types of exchanges are incredibly valuable.

Why is Switzerland's biopharma climate so favorable?

Switzerland has a very long biopharma tradition and many cantons in the country have some kind of bio-innovation or start-up park. Due to the favourable legal and economic framework (including tax conditions), it is well suited to biotechs. It's also very easy and quick to launch a new start up. Moreover, there are good incubators and networks – and, of course, the Swiss Biotech Association aims to help too!

For talent in the biopharma industry, there are many different opportunities in Switzerland because there are so many companies here. There is a lot of cross-fertilization as talent moves between different companies too.

What is your advice for others in industry who want to move into leadership?

It's very difficult to plan a career. There are many things that you can do to influence things, but there are also special moments that are not entirely in your hands, where you depend on the trust of others and your network.

I have three daughters – two of them are already in university – and I always tell them to find something you do with passion and something that is difficult; show the world that you challenge yourself, and that you can do difficult things. People who challenge themselves over and over again will be able to make their dreams come true.

And do you have additional career aspirations or even dreams?

In recent years, I've been involved in

biotech board work. I enjoy what I do, and I especially like the combination of working with the association and with industry.

I'm also interested in what comes next for biosimilars. We have found a way to bring microbial and mammalian products to larger patient populations – perhaps next there will be more complex biosimilars, such as ADCs. And then further in the future, what about cell therapies?

What is the most important lesson you've learned over your career?

I think it's important to be close to your purpose and what you believe in – and also to realize that you are not just somebody who's working; you're also a private person with a family and friends. Being in biopharma allows you to bring that all nicely together. When you have a career where you can connect your purpose and be yourself, you will be able to give so much more.

When you were younger, did you ever imagine working in the (bio)pharma industry?

The motivation to make the world a better place certainly always resonated strongly with me; I studied environment and environmental sciences as a master and PhD, specializing in the life sciences industry for the latter. When I got started in biopharma, it was for an environmental role, but then I moved to health, safety, and environment, before taking up roles in quality, manufacturing, and the supply chain. By now, I know a lot about different functions in the industry!

I may not have predicted it – but it's great to work in an industry that makes medicines. My mother died young from multiple sclerosis (MS), and, for a time, I worked for Biogen, which is very focused on MS. Now, I'm at Sandoz, we bring a more affordable biosimilar version of an originator MS therapy to the market... Sometimes things in your life come together in an unexpected way.

Enabling a Healthier World

Lonza

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