APRIL 2021 # 74

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A Roadmap for Access

We must secure sustainable markets to ensure patient access to generic and biosimilar medicines

The pandemic has presented a unique challenge to healthcare systems and infrastructure, including the generic drug supply chain. Generic drug manufacturers have met this challenge, ensuring a stable supply of life-saving medicines for patients throughout the pandemic. However, the long-term sustainability of the generic and emerging biosimilars medicines market faces threats. Policymakers should consider and address the unique challenges facing generics and biosimilars to maintain long-term access to cost savings for patients. In its latest paper, Securing Sustainable Markets, the Association for Accessible Medicines (AAM) announced a series of policy proposals intended to ensure patient access to lower-cost medicines (1).

Generic drugs face competitive imbalances in the market, such as a highly consolidated drug purchasing system controlled by a few major organizations, combined with ill-advised government policies. These policies have historically led to high rates of price deflation and low reimbursement, sometimes driving manufacturers out of the market. For example, Medicaid imposes an inflation penalty that penalizes generic manufacturers who experience price variability due to fluctuation in purchasing patterns.

And consider this: the growing categories of specialty and complex generics and biosimilars offer critical new savings opportunities for patients, along with financial sustainability for manufacturers; however, patient adoption of such new, lower-cost alternatives is unfortunately hindered by government and payer policies that perversely reward the use of high-cost brands over lower-priced generic or biosimilar competitors. Policies such as the brand drug Coverage Gap Discount Program and the use of brand drug rebate traps encourage plans to restrict patient access to generics or biosimilars in favor of higher-cost brands.

Note that Medicare Part D formularies are slower in covering newly approved first generics compared with commercial health plans, in spite of the lower cost of generics. Similarly, Medicare Part B reimbursement policies discourage biosimilar adoption, even though biosimilars are 30 percent less expensive (on average) than reference brand-name biologics.

As more FDA-authorized COVID-19 vaccines are distributed and administered, we'll all be hoping for a speedy rebound from the pandemic. Certainly, generics will have played a key role as a bridge to those vaccines. AAM calls for updated government policies that value generic and biosimilar competition, do not penalize continued production of older commoditized generics, and create opportunities for future patient savings.

Craig Burton
Vice President, Policy at the Association for Accessible Medicines

Reference

1. *AAM, "Securing Sustainable Markets," (2021). Available at www.secureourmeds.org/securing-sustainable-markets*

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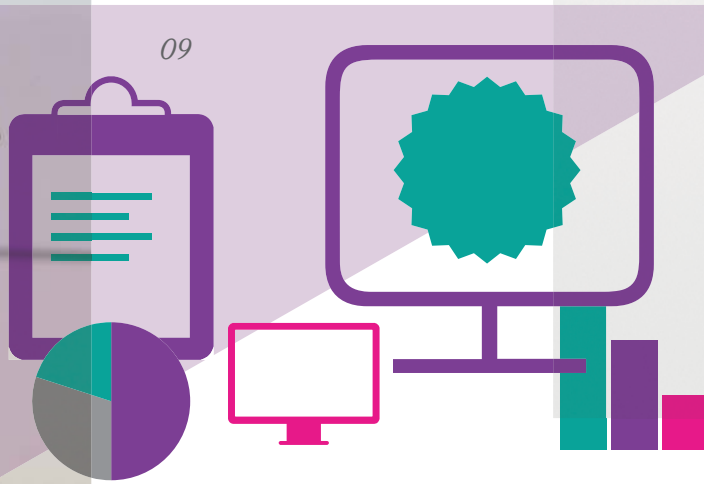

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Dorcas Osei-Safo

A Little Less Conventional

Researchers prove the effectiveness of traditional herbal medicines against neglected tropical diseases

Can traditional medicines be standardized to help create affordable drug access in low- and middle- income countries? Researchers at the University of Ghana, certainly think so and have published data that indicates how herbal preparations can be successfully used for the treatment of neglected diseases (NTDs) like schistosomiasis (snail fever), onchocerciasis (river blindness), and lymphatic filariasis (elephantiasis) (1).

"The use of traditional medicines as therapeutic agents is generally not accepted by pharma," says Dorcas Osei-Safo, associate professor and researcher at the University of Ghana. "There are grave concerns about the lack of established evidence of safety and efficacy, as well as data on dosage, good manufacturing practices, quality control, and standardization."

However, Osei-Safo explains that, among the Ghanaian public, traditional medicines are widely used – particularly in rural areas – as they are cost-effective alternatives to conventional medicines and are thought to have few adverse effects. With the aim of improving access, Osei-Safo and her colleagues decided to explore whether these plant-based medicines could make a difference to patient care.

After screening multiple plant and solvent combinations, the team found 15 dried herb extracts that were effective against their target NTD – but they also discovered something unexpected. "Though the extracts certainly demonstrated different levels of activity against their target disease, many of them were more effective against other tested NTDs – much to our surprise!" says Osei-Safo. The majority were most active against Trypanosoma brucei brucei, a parasite that causes sleeping sickness. The researchers believe the findings suggest that traditional medicines deserve further exploration.

So far, only one active extract has been subject to complete bioassay fractionation. The remaining identified active extracts are currently under investigation. "We hope to come up with a couple of promising compounds that could be further developed into potential drugs," says Osei-Safo. But the team's goals are not limited to molecular isolation of traditional medicines for pharmaceutical development; they are also exploring how they can develop standard protocols to ensure the safety and effectiveness of the original traditional medicine.

Reference

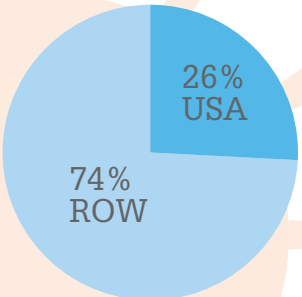
1. *EB Twumasi et al., PLOS Negl Trop Dis, 14, 12 (2020). DOI: 10.1371/journal.pntd.0008919*

INFOGRAPHIC

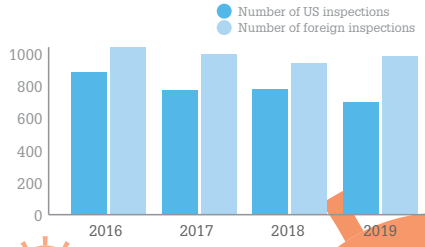
Beating the Backlog

How well has the FDA managed its inspections at home and abroad during the pandemic?

Manufacturing sites

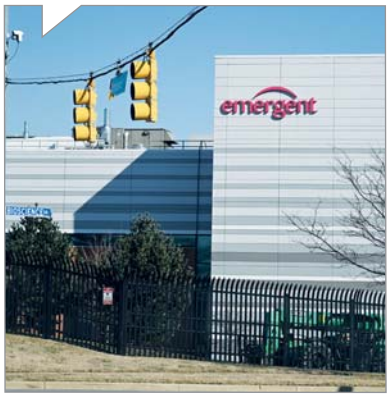


Inspections at home and abroad



BUSINESS IN BRIEF

Manufacturing mishaps, improper practices, and regulatory recommendations… What's new in business?



- The US Department of Health and Human Services has stripped Emergent BioSolutions of its responsibilities for the manufacture of COVID-19 vaccines and handed over production to J&J. The move comes after the CMO's Baltimore-based plant, Bayview, was found to have mixed up two ingredients used in the AstraZeneca and J&J COVID-19 vaccines – resulting in the production of 15 million botched doses.
- A letter penned by the White House's Special Counsel, Henry J. Kerner, outlines claims from a former FDA employee and whistleblower, who alleges that regulatory misconduct led to several inspections being improperly downgraded and violations overlooked. The whistleblower claims that employees soiled themselves rather than take bathroom breaks, allowing them to move between manufacturing areas without having to remove their sterile gowning. This led to the improper disposal of uniforms in biohazard bins. In the letter, Kerner said, "I am troubled by many aspects of this matter. I urge the agency to closely examine compliance issues like these."
- The MHRA and EMA have concluded investigations into the use of the AstraZeneca COVID-19 vaccine. The vaccine has recently come under public scrutiny as cases of rare blood clots were reported after administration. The EU regulator argues that the benefits of use outweigh the risks given the low number of reported cases. However, the MHRA has recommended that alternative vaccines are used in people under the age of 30. Other countries will use alternative vaccines in those under the age of 50.

The Whey of Things

New guidance outlines the safety of animal-derived excipients

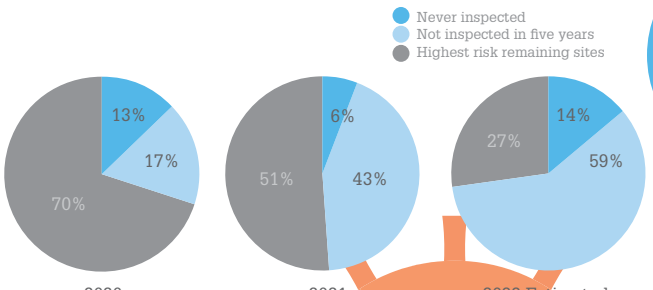
Responding to regulators' calls for clearer guidance on the risks of excipients to patient health, the International Pharmaceutical Excipient Council (IPEC) Federation has published a position paper outlining the safety of the lactose-derived excipient whey (1). A natural polymer, whey is used in various oral dosage forms for its drug-binding capabilities – but some regulatory authorities consider ingredients from human or animal sources to have high chemical and biological risks when incorporated into oral preparations.

IPEC argues that the risk profile of pharmaceutical-grade whey is low because it is sourced from lactose manufactured to GMP standards. Historically, the excipient has also proven to be nontoxic with a good safety profile. The council now hopes that this classification will "result in fewer dossier requirements for lactose when applying for marketing authorizations" – making medicines that contain it more readily available.

Reference

1. *IPEC Federation (2021). Available at https://bit.ly/3d3H6nA.*

COVID-19 Consequences



60% fewer inspections took place in 2020 than the two years previous

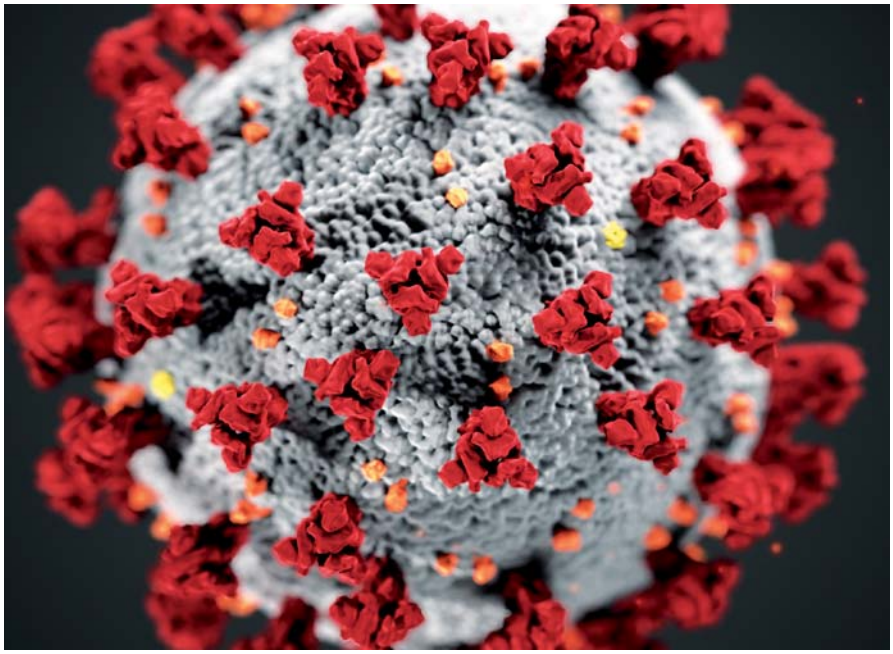
Barriers to inspection

✖ Availability of overseas inspectors
✖ Differences in inspection procedure in the US and abroad
✖ Language barriers

Source
United States Government Accountability Office, "FDA's Future Inspection Plans Need to Address Issues Presented by COVID-19 Backlog" (2021). Available at https://bit.ly/3rOTGx5.

Protecting the Vulnerable

How do COVID-19 vaccines impact at-risk patients?



COVID-19 vaccinations have begun worldwide, but how effective will they be for at-risk groups, such as immunocompromised patients? Researchers from several British academic institutions have launched a trial, OCTAVE, to better understand how current iterations of COVID-19 vaccines will impact vulnerable populations (1).

According to Pam Kearns, Professor of Clinical Paediatric Oncology at the University of Birmingham, and Director of both the Cancer Research UK Clinical Trials Unit and the Institute of Cancer and Genomic Sciences, studies over the last 12 months have shown wide variation in immunocompromised patients' responses to COVID-19. These patients' vulnerability to the virus increases the importance of vaccination, but their conditions also make them more likely to exhibit altered immune responses to the vaccines.

"Their response to the virus can be attributed to their underlying disease, its associated immune dysregulation, or their use of immune-modifying medications," Kearns says. "Trials that evaluated the efficacy of the SARS-CoV-2 vaccines predominantly recruit individuals without chronic diseases. Therefore, we do not know the effectiveness of the immune response and its durability in patients with impaired immune systems."

Through the OCTAVE trial, the collaborative team will evaluate immune responses to COVID-19 vaccines, including the BioNTech/Pfizer, Oxford/AstraZeneca, and Moderna vaccines. The team aims to recruit unvaccinated patients, as well as those who have received their first dose and who live with end-stage kidney disease, liver disease, some forms of cancer, immune-mediated rheumatic diseases, or a history of solid organ transplant.

The team is not short of volunteers. "Trial inboxes have been inundated with hundreds of messages from patients highly committed to helping us find the answers to our questions. Though not all are eligible, we aim to disseminate our results to inform the wider public as soon as they are available," says Kearns.

Reference

1. *University of Birmingham (2021). Available at: https://bit.ly/3vTvTyB.*

Lowering Chromatography Costs

An old technique – resurrected and repurposed for modern bioprocessing

Though useful in the treatment of various chronic illnesses, the price of many monoclonal antibodies negatively impacts their accessibility. "Every year, individuals and insurance companies spend upwards of US$100 billion on antibodies, with costs to treat a single patient often exceeding $50,000," said Andrew Zydney, Bayard D. Kunkle Chair, and professor of chemical engineering at Penn State, in a statement (1) . The reason? Affinity chromatography, the process used to separate a desired antibody from a solution, relies on chromatography columns that can cost up to $10 million each.

Aiming to lower the cost of these much-needed medicines, Zydney and his colleagues applied a 70-year-old protein purification method used for plasma processing to the development of antibody drugs (1). The team added zinc chloride and polyethylene glycol to separate a target antibody in solution – a cheaper, time-effective alternative to conventional practices. This progress has left the team hoping that the process can be scaled up to help patients access these medicines at affordable prices.

Reference

1. *AL Zydney et al, Biotechnology Progress (2020). Available at: https://doi.org/10.1002/btpr.3082.*

IMAGE OF THE MONTH

Benchtop Buddy

Helping to accelerate drug manufacturing, a benchtop robot developed by collaborators at Clemson University and Nephron Pharmaceuticals is put to use for the fill and finish of sterile syringes.
https://bit.ly/3civA8r Credit: Clemson University

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QUOTE of the month

"We are at a critical point in human history. We now have the tools to dramatically reduce or eliminate the risk of future epidemics and pandemics. We must invest now in the vaccines and biologic countermeasures that we need, while linking these investments with commitments to equitable access."

Richard Hachett, Chief Executive Officer, CEPI
https://bit.ly/2OCpeHY

In Silico Insight

A report shows the benefits of synthetic data for clinical trials

A report published by Accenture and Phesi shows that synthetic data can help drive faster, more efficient clinical trials. According to the document, AI systems that analyze electronic medical records and track patient outcomes allow for new data on trial protocols and results to be generated easily. However, the collaborators also point out that there are barriers to implementation. Often, pharma companies do not have access to data from varied sources and can also refuse to share the data they generate with others, preventing accurate statistical analysis.

"Once the availability of data is addressed, an investment into technology, skills, and leadership is a must," the report states. "Pharma companies need to do more to identify and adopt advanced technologies to work with the data needed for in-silico clinical trials. R&D leaders will have to be bold in defining their next steps."

Read the full report at https://accntu.re/31u91HX

Fit for the Future

We catch up with Samsung Biologics about easing tech transfers and preparing plants for the future

Since its founding, Samsung Biologics has gone from strength to strength. Recently, the company partnered with Eli Lilly to help boost Lilly's COVID-19 antibody manufacturing capacity. Samsung is also building a "Super Plant" that will incorporate automation and emerging technologies. We caught up with James Choi, Senior VP and Head of Marketing and Investor Relations from Samsung Biologics, to get more details.

What's the background between Lilly and Samsung Biologics?

We entered into a long-term manufacturing partnership agreement with Lilly back in May 2020 to address the urgent demand for COVID-19 treatments worldwide. Despite the global challenges of securing stable supply amid the pandemic, we were able to manufacture and deliver an initial supply of APIs within five months of contract signing, as well as reduce the timeline for tech transfer to less than three months. This was all possible because of great collaboration between us and Lilly.

How has demand for manufacturing capacity changed since the pandemic began?

Even before COVID-19, we'd seen an increasing trend in the demand for biomedicines manufacturing. The pandemic has definitely intensified this demand. We've signed numerous contracts with global biopharma companies to manufacture a variety of drugs, including COVID-19 treatment candidates and expanded biologics products, with orders totalling over US$1.5 billion (1.8 trillion KRW) in the first half of 2020 alone – a 150 percent increase over our total revenue last year.

How did you shorten the tech transfer timeline with Lilly?

Thanks to the close communication and coordination between our two teams' technical, quality, supply chain, and regulatory experts, we reduced the tech transfer timeline from six months to three. Biopharmaceutical technology transfer requires careful planning and evaluation to meet the scale-up and GMP manufacture timelines. Specifically, we believe the timing of facility fit and gap assessments is critical to the success of the technology transfer, as well as to avoid unexpected risks and delays to the manufacturing schedule.

Samsung Biologics has also started work on Plant 4 – why is it dubbed "Super Plant"?

Plant 4 will be the world's largest

biopharmaceutical manufacturing facility of its kind, with a total of 256,000 L manufacturing capacity. Upon completion, our company is expected to be accountable for one-third of the total global bio-CMO manufacturing capacity, offering a combined sum of 620,000 L from our site in Incheon, South Korea.

We chose a modular design to allow flexibility for certain parts of the plant to begin manufacturing activities by the end of 2022, with the goal of commencing full operations in 2023.

What do you think is important to ensure any new facility is truly fit for the future?

Now, more than ever, it's vital for biopharmaceutical companies to evolve digitally through innovative technologies. For our new Plant 4, and across our existing plants, we have begun a digital transformation initiative to enable real-time client access to their quality records and documentation while ensuring client confidentiality and security. Our systems are fully implemented with data integrity and cybersecurity, and Samsung Biologics is the first CDMO to be ISO 27001 certified across all of our existing plants. It's also imperative that manufacturing facilities are equipped to cater to clients' needs and support them throughout the drug development process. Our Super Plant will provide a full range of CDMO processes for a complete one-stop service, including early-stage development capabilities and large-scale commercial manufacturing with a full QC lab.

In My View

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

What's in Your Capsids?

Are your capsids full, half full, or empty? We need better analytical techniques to tell us the answers to these crucial questions in the development of gene therapies.

By Lori Stansberry, Senior BioPharma Marketing Manager at Thermo Fisher Scientific

It's just over 30 years since the first approved gene therapy procedure was performed – and I'm sure we're all amazed at how the field has progressed since then. The FDA expects approvals for cell and gene therapy products to reach around 20 per year by 2025 (1). A key component enabling the growth of the field of gene therapy is recombinant adeno-associated virus (AAV) vectors. There have been three recombinant AAV-based gene therapies approved for commercial use so far (2), and there are hundreds of active clinical trials worldwide for a variety of diseases.

As development of gene therapies increases, there is a growing demand for accurate and efficient techniques for characterizing AAV vectors. Many existing methods for analyzing AAV vectors, particularly for determining the full/empty capsid ratio, are labor-intensive and time consuming. Analytical methods using anion exchange (AEX) chromatography, however, are supporting the analysis of AAV capsids and could be a key technology for further advancing gene therapies.

Viral vector characterization is essential for assuring product quality. Critical quality attributes (CQAs) include viral potency, identity, quantity, process residuals (i.e., Triton and deoxiribonuclease), aggregation, empty capsids, capsid protein content, and product safety. To meet purity requirements the proportion of empty, partial, and full AAV capsids must be determined. Unsurprisingly, full capsids are required for therapeutic efficacy; empty capsids, which do not contain genetic material, or partial capsids, which contain only a fragment of the genetic material, are simply by-products of AAV production and can negatively impact product efficacy and safety – potentially producing adverse reactions, such as an immunogenic response in the patient.

There are various analytical methods for characterizing capsid levels in the laboratory, including transmission electron microscopy (TEM), analytical ultracentrifugation (AUC), charge detection mass spectrometry, and UV spectrophotometry. The two main methods are TEM and AUC. TEM involves a sample vitrified by rapid freezing to preserve the structure of a biological specimen. When imaged, there is a clear difference in structure between full and empty particles. The AUC method distinguishes and quantifies the different AAV capsids either by density (sedimentation equilibrium) or mass (sedimentation velocity).

As AAVs are relative newcomers in gene therapy, the industry has not yet decided upon the most effective method of analysis. Certainly, existing

methods for determining the full/empty ratio of AAV capsids have limitations; for example, TEM provides direct visualization and counting of the empty and full particles, but quantification heavily relies on image quality and field selection.

And although AUC has excellent resolution and is highly accurate, it often requires a dedicated facility and specially trained analysts, who must spend hours on data interpretation. Moreover, AUC also consumes hundreds of microliters of valuable samples.

In short, TEM and AUC are both low throughput – and neither is readily scalable.

In my view, AEX chromatography is a useful technique for the analytical toolbox. When genetic material is encapsulated in the capsid, the surface charge on the particle changes. This physiochemical difference between full and empty capsids makes them ideal for analysis with AEX chromatography methods. AAVs are also small (20-25 nm) and suitable for both traditional and monolithic columns.

The AEX chromatography method requires only several microliters of material – clearly a real benefit when gene therapy samples are so precious. Furthermore, no sample preparation is needed, which simplifies the analysis and increases throughput.

Historically, use of the AEX method for separation of empty, full, and partial capsid was less than optimal due to analysts narrowly exploring anion exchange column chemistries. For example, a user may begin method development with a column that would be recommended for nucleotide analysis because this would work well for characterizing genetic material inside the AAV. However, this same column chemistry may not be best suited to separate empty, partial, and full capsids. Today, chromatographers have learned they need to search across multiple column chemistries to find the solution that provides the best resolution for empty/ full capsid separation.

Right now, AUC provides the better resolution, but I believe that ongoing developments with AEX column chemistries and chromatography systems make it a technology to watch for the future. Chromatography systems are already up and running in the QC environment for other processes and specialist expertise is not needed. Also, chromatography lends itself well to automation opportunities, opening the door for high-throughput capsid analysis, ultimately providing a more cost-effective way of speeding up product development and reducing time to market.

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1. *FDA, "Statement from FDA Commissioner Scott Gottlieb, M.D. and Peter Marks, M.D., Ph.D., Director of the Center for Biologics Evaluation and Research on new policies to advance development of safe and effective cell and gene therapies," (2019). Available at https://bit.ly/3ryl9mp*
2. *FDA, "Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)," (2020). Available at https://bit.ly/3t728b6*

Jumping into the Digital World

In today's world of home working and remote business operations, secure digital technologies are more essential than ever. Pharma can no longer sit on the sidelines.

By Jason Lacombe, Chief Executive Officer of Veratrak

COVID-19 has accelerated digital adoption of new technologies moving pharmaceutical and life sciences companies away from paper-based processes and towards electronic data capture. Rightly or wrongly, many pharma companies have traditionally preferred paper-based systems for recording and sharing data, which has exposed inefficiencies. For example, one customer explained to me how, pre-COVID-19, their suppliers were adamant that they had to always supply a physical document. The document would need to be printed, physically signed, scanned, and then returned. Now, many employees are working remotely and not all have access to printers and scanners; as a result, companies have been forced to adopt new software and platforms that allow business to continue as normal.

In the pharmaceutical and life sciences industry, traveling to a supplier or partner site to perform an audit has also changed, with regulators and market authorization holders performing these critical assessments virtually. In line with recent EMA, FDA, and MHRA guidance, both parties involved in the virtual audit have had to put digital solutions in place. Gone are the days when you could take the auditors to a boardroom and present them with endless boxes of paper documents to prove compliance. Instead, companies have rolled out new software tools allowing them to share electronic documents, such as, SOPs, training materials, and quality documentation directly in a software platform, and seamlessly collaborate and communicate with all parties involved in the audit.

"Gone are the days when you could take the auditors to a boardroom and present them with endless boxes of paper documents to prove compliance."

Although digitization is new to pharma, it is not new to other industries. Many companies elsewhere have embraced digital technology, and software companies have spent decades developing flexible and agile platforms. Operating in a GxP environment such as pharma means that industry agnostic software platforms are required to be validated before going live. The speed required to adopt new technology because of COVID-19 has meant that pharma-specific software platforms that provide validation out of the box are taking center stage.

We don't know how long the pandemic will last for but, even after it has ended, we will not return to the old ways of working. Many companies are satisfied with flexible working and will allow this to continue – and there are costs to be saved; downsizing office space, for example. But digitization is not just about enabling remote working. In my view, digital tools allow for significantly improved efficiency and cross-company collaboration. Relying on emails and non-validation file sharing tools for collaborating with your partners leads to poor document visibility, versioning issues, delays, lost information, and poor cybersecurity. One of the most common tools for sharing documentation is email, but emails are a popular entry port for cyber attacks, such as PDF malware. What looks like an uploaded PDF in one's inbox can carry malicious JavaScript code; once an employee opens the attached PDF, it comprises the entire network. In recent years, a number of pharmaceutical entities, including Merck, Dr. Reddy's, and even the EMA, have been hit with cyberattacks.

One of the digital technologies

"We don't know how long the pandemic will last but, even after it has ended, we will not return to the old ways of working."

I am most excited by is distributed ledger technology – often known as blockchain – because it ensures data integrity when documents are being shared. Using a blockchain architecture to underlie all external exchange of data and documentation across your supply chain significantly reduces the risk of cyber attack on your organization. Blockchain is a distributed ledger. A ledger is just a way of record-keeping. It is a reliable way of keeping transactional information and understanding who has performed an action, such as who has uploaded something, downloaded something, or reviewed something. Instead of a single ledger with a single point of failure, there are multiple ledgers that are continuously updated. To compromise the entire distributed ledger, you need to take over the majority of ledgers within the network – and that's close to impossible. With so many people working from home, we've seen an increase in companies looking into blockchain technology – as well as other digital solutions to product their IT infrastructure as more organizations share sensitive GxP information regularly outside their four walls.

As a result of COVID-19 accelerating the use of digital technologies across the pharma industry, I hope that companies will be more proactive when it comes to adopting new technology in the future. By piloting a new process and technology like blockchain in parallel with a current process, you can measure efficiency gains and other benefits more readily. Once you have the results at the end of a pilot, you can build a business case for full implementation more easily and begin scaling up this new technology.

Riding the (Nucleo)Tidal Wave

DNA manufacturers must pick up the pace to support the genetic medicine revolution

By Karen Fallen, Chief Executive Officer of Touchlight DNA Services

The genetic medicine sector is booming. Before the pandemic hit, research and commercialization of cell and gene therapies (CGTs) was advancing at pace and, despite slight disruption in 2020, the market is still expected to reach US$13.23 billion by 2023 (1). But COVID-19 has also highlighted the immense potential of other genetic medicines, specifically prophylactic vaccines. The exceptional circumstances over the past year have accelerated the emergence of novel nucleic acid vaccine technologies, and motivated development and manufacture at an unprecedented scale. The first mRNA vaccine ever approved for human use is already being distributed by the millions, and a second generation of DNA vaccines is also in the pipeline.

The pandemic has been a proving ground for these new technologies and is expected to result in tremendous industry growth. The number of indications that could benefit from this advancement is vast, including a wide range of infectious diseases. Moderna, for instance, is working on mRNA programs for HIV, flu, and the Nipah virus. There is also a lot of activity in the oncology space.

The demand for millions (or billions) of doses of these pioneering vaccines sparks the question of how we can deliver genetic medicines at scale. We have seen regulators working to significantly shorter timeframes, and large-scale collaborations have been announced worldwide, with big pharma working with biotechs and CDMOs to combine strengths, expertise, skills, and technologies. There has been considerable financial investment from both big pharma and governments, including the Biomedical Advanced Research and Development Authority (BARDA), Defense Advanced Research Projects Agency (DARPA), and Coalition for Epidemic Preparedness Innovations (CEPI) programs, which have provided major support for the industry. Manufacturers are also committing to sizable capacity expansions to meet the growing needs. Despite all these efforts, however, we are already seeing how fragile the supply chains are, with major players reporting delays in delivery, primarily due to production issues.

Genetic medicines, such as nucleic acid vaccines and cell and gene therapies, are heavily reliant on a sufficient and adequate supply of DNA. With the remarkable expansion of both fields, the demand for DNA today is extraordinary. Unfortunately, conventional plasmid DNA manufacturing technologies are not well suited for rapid scale-up. E. coli fermentation is slow, expensive, and limited by a lack of capacity. Batch failures are not uncommon, and antibiotic resistance genes can be present in the final product. These factors bring significant challenges for the rapid, scalable response required in a pandemic situation, and DNA production has, therefore, become a significant bottleneck. One approach (and my company's approach) to solving these challenges is to use synthetic DNA manufacturing, which enables significantly accelerated production, rapid scale-up, greater reliability, and lower capital and costs.

"The demand for millions (or billions) of doses of these pioneering vaccines sparks the question of how we can deliver genetic medicines at scale."

We must remember that, when compared with the rapidly maturing genetic medicine industry, DNA manufacture is still in its infancy. If we are to support the growing sector, we must embrace new approaches and technologies, maintain focus, and commitment to improving the supply chain, and continue funding beyond the pandemic. Collaborations will also be crucial for future success. We must ensure that we make the most of the current momentum by working together on the advancement of genetic medicine manufacture.

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Filling: How to Find the Right Setup

Ready-to-use containers for sterile injectables can significantly improve total costs of ownership for pharmaceutical companies

By Robert Linder

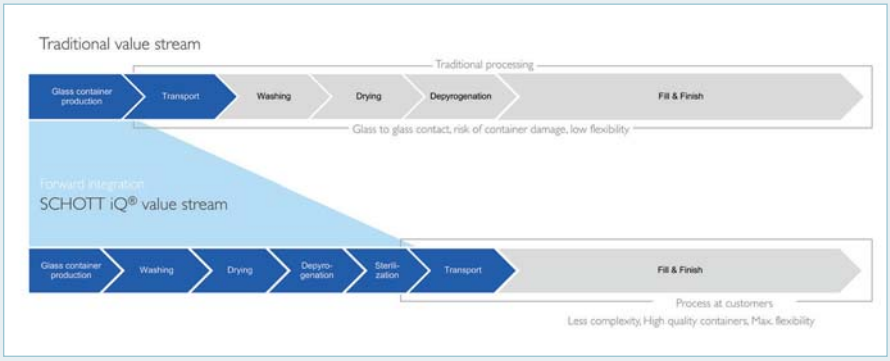

Figure 1: Value streams for traditional and RTU filling.

Pharmaceutical operations are optimized to produce high quality drugs reliably over a period of decades. Introducing innovations into manufacturing can lead to long-term risks, so any necessary changes demand thorough consideration. In particular, medical safety and economic viability have to be analyzed in parallel when choosing the primary packaging and the corresponding fill and finish concept. Assessing total cost of ownership is a good approach to gauge the economic viability of a project that spans several years, particularly when choosing between ready-to-use (RTU) and traditional containers. SCHOTT has developed a straightforward model to help customers select the ideal filling setup for their operation – based on an analysis of the total costs of ownership.

Exploring the trends

The pharmaceutical industry is at a pivot point. Of the more than 4500 injectable drugs in the pipeline, approximately 80 percent are biologics (1). These are mainly targeted towards smaller patient populations, addressing rare diseases or enabling a more patient-centric therapy. At the same time, the more rapid market entry of biosimilars increases the importance of drug life cycle management. Batch sizes are getting smaller, changeovers on fill-and-finish lines are becoming more frequent, and adaptations in primary packaging container formats are more likely. These trends require high flexibility, which can be provided by pre-washed, pre-sterilized standardized RTU containers. However, there are cases where a switch from traditional to RTU containers is not economically feasible. To account for this added complexity, we must gain a thorough and holistic understanding of all options and parameters.

RTU vs traditional containers

Unlike traditional solutions, RTU containers come washed, depyrogenated, and sterilized, which means they can go straight into the filling operation, eliminating many steps for pharma companies (see Figure 1). The containers are delivered in a nest-and-tub configuration, which also prevents glass-to-glass contact, and reduces defects, such as scratches, breakage, and particles. The nest-and-tub concept was first developed for RTU prefilled syringes and has been the industry standard for around 30 years. Today, SCHOTT offers the whole range of primary packaging containers in its SCHOTT iQ® platform within a harmonized and standardized secondary packaging. Pursuing a single, standard method of filling allows manufacturers to maximize the utilization of each filling line (2). And that leads to greater flexibility, which is further enhanced through increasingly flexible machine concepts.

The traditional value stream for filling pharmaceutical containers is relatively straightforward. Glass containers are produced and transported to the pharmaceutical manufacturer, where they are fed into the filling line, washed, dried, and depyrogenated to ensure the containers are safe and sterile, ready for the fill-and-finish process. As all container types have different dimensions, separate filling lines are required in individual cleanrooms for vials, prefilled syringes (PFS), and cartridges. This translates into higher initial investments, greater operating costs, and reduced flexibility. In addition, the glass-to-glass contact throughout the process carries a risk of defects, breakage, and particle generation.

With RTU containers, the value stream is forward integrated to reduce complexity and maximize flexibility for the pharmaceutical company, as all the containers fed into the filling line have already gone through a standardized, validated and cost-optimized washing and sterilization procedure. Because the SCHOTT iQ® platform is built on compliance with all relevant industry standards, the different container formats can be filled on a single filling line, which significantly reduces the initial investment in machinery and cleanroom capacity.

Counting costs

Economic viability is best assessed by looking at the total cost of ownership, which includes all initial and recurring costs throughout the whole project lifetime. For fill-and-finish operations in

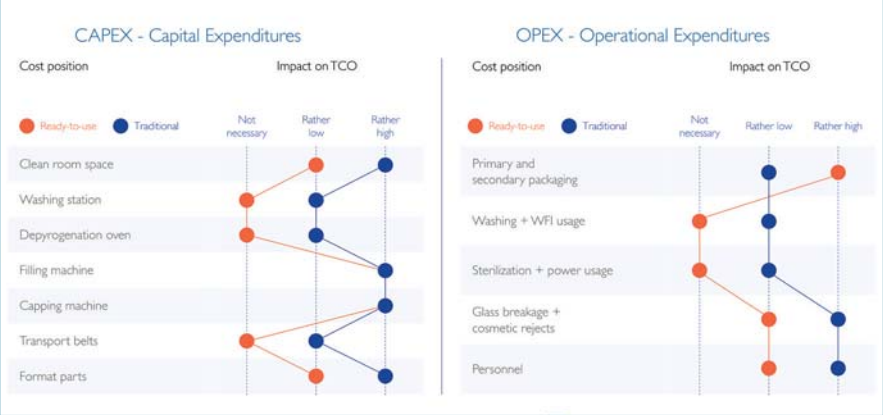

Table 1: Cost types and impact of cost positions of traditional and RTU filling.

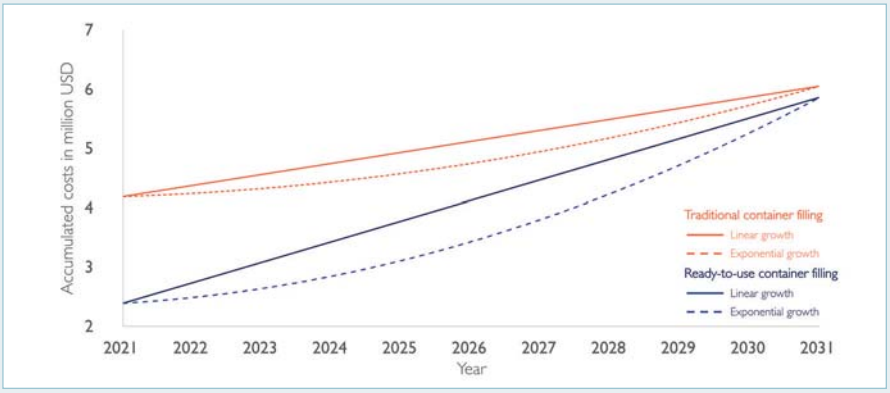

Figure 2: Growth scenarios for total costs of ownership for traditional filling and ready-to-use filling. Note that this case is illustrative only.

the pharmaceutical industry, SCHOTT developed a straightforward model and calculated the total cost of ownership for different scenarios using RTU and traditional containers. The model allows us to guide customers to find the right packaging configuration for their business case.

SCHOTT's model is based on the typical costs that occur during a pharmaceutical fill-and-finish operation, as listed in Table 1. All capital expenditures (CAPEX) are taken into account, with a depreciation rate appropriate to the project lifetime, such as the cost of the filling line and the washer, and setting up the cleanroom space. The recurring operational expenses are also included, such as primary packaging or labor costs. By comparing typical relative values between traditional and RTU filling, the impact of the individual cost positions becomes apparent. Though filling traditional containers is associated with lower expenses for primary packaging, RTU filling offers advantages of no direct costs for washing and sterilization, as well as lower costs associated with the risk of glass breakage and cosmetic rejects caused by glass-to-glass contact. Similarly, fewer personnel are needed to operate the higher automated RTU filling lines.

Building the business case

When trying to decide which filling strategy to follow, all costs have to be carefully balanced against each other. In SCHOTT's TCO model, the above-mentioned costs are determined based on several simple questions:

- Where will the factory be?
- How long is the project duration?
- Which and how many containers of different types will be filled?
- Which machines will be used?
- How many shifts will be in operation?
- Will it be a small batch or campaign production?

With these inputs and database values for the different cost positions, the total cost of ownership can be modeled for different growth scenarios. Figure 2 shows an exemplary case calculated using this model. The project, starting in 2021 with an initial investment of around US$2 million, is modeled with a linear growth (solid line) and an exponential growth (dashed line). It can be seen that for both growth scenarios, filling only RTU components is cheaper at the end of the 10-year project timeframe. The economic advantage of filling RTU containers can be partly attributed to the higher costs associated with the need to buy multiple filling lines for the different container types and greater cleanroom space requirement.

Deciding on a fill and finish concept that needs to be economically beneficial for several years or even decades is becoming more challenging, with new container options entering the market and the increased need for flexibility. Looking at the total cost of ownership helps obtain a clear picture of the machine and container combination that facilitates operation throughout the lifetime of the project. And SCHOTT's straightforward TCO model – based on extensive knowhow of an industry leader – helps you come to a sound conclusion.

Dr Robert Linder is Product Manager at Schott

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the Medicine Maker

POWER LIST

Welcome to our annual celebration of the great and inspirational minds that contribute to the development and manufacture of medicines, including small molecules, biopharmaceuticals, and advanced therapies

By Stephanie Sutton, James Strachan, and Maryam Mahdi

Putting together last year's Power List was a surreal experience; at the time, we were just getting to grips with how COVID-19 was affecting the world and changing our everyday lives. We faced a very uncertain future – especially as we all knew that new vaccine and drug development typically takes around ten years.

Now in 2021, lockdowns remain in place in many countries and the death toll continues to rise; approaching 3 million as of early April 2021. Severe lessons have been learned by governments that failed to respect the dangers of the virus. And pharma too has learned many lessons in terms of securing supply chains, adapting operations to suit social distancing, and working faster than ever before to research and develop new therapeutic options for a new virus.

The pandemic is not over – and won't be for some time – but there are reasons to feel optimistic. Effective vaccines have been approved by various regulators for emergency use, existing drugs are being repurposed to help patients with severe COVID-19, and new drug development is vibrant. Small molecules, biopharmaceuticals, and even cell therapies are all being explored as potential medicines to combat COVID-19. The industry has genuinely outdone itself. And alongside interventions against COVID-19, others in the industry continue to work tirelessly to address other crucial areas.

For 2021, we present the top 20 inspirational medicine makers in three different categories: Small Molecules (page 21), Biopharmaceuticals (page 26), and Advanced Medicine (page 32).

Want to share this list with a colleague? It can be accessed online for free at https://themedicinemaker.com/power-list/2021

SMALL MOLECULES

Top 20

PHIL S. BARAN

PROFESSOR AT SCRIPPS RESEARCH

Baran has received numerous awards and accolades for his contributions to both industry and academia. His ambition is to contribute to the development of organic chemistry by educating students, inventing new tools and strategies, and using these new technologies in the pharmaceutical space to accelerate the development of small and large molecule medicines. "The use of biologics and oligonucleotide based therapies will continue to grow in popularity (for good reason) but, when the same outcome can be achieved using orally bioavailable small molecule therapies, those are almost always preferable from the standpoint of cost, simplicity, and worldwide availability."

ROSS T. BURN

CEO AT CATSCI LTD

After completing his PhD in 2007, Ross joined AstraZeneca as a Senior Analytical Chemist in process R&D. Burn helped launch CatSci Ltd in 2011 and became its Chief Executive Officer in 2015. "Even though new therapeutic modalities are on the rise, there are still limitations to their efficacy, scalability, patient tolerability, and wider adoption by healthcare providers. Small molecule therapeutics will always play a key role in combating diseases due to their relative affordability, greener profile, and well-understood development processes. Additionally, with advances in chemistry, the industry can uncover new molecular entities with unprecedented target activity that can be manufactured at a speed and cost not feasible 10 years ago."

KELLY CHIBALE

NEVILLE ISDELL CHAIR IN AFRICAN-CENTRIC DRUG DISCOVERY & DEVELOPMENT AND SOUTH AFRICA RESEARCH CHAIR IN DRUG DISCOVERY

Chibale is a Professor of Organic Chemistry at the University of Cape Town (UCT). He is also a Full Member of the UCT Institute of Infectious Disease & Molecular Medicine, a Tier 1 South Africa Research Chair in Drug Discovery, founding Director of the South African Medical Research Council (SAMRC) Drug Discovery & Development Research Unit at UCT, and the Founder and Director of the UCT Drug Discovery and Development Centre (H3D). In 2018, he was recognized by Fortune magazine as one of the World's 50 Greatest Leaders and, in 2019, he was named as one of the 100 Most Influential Africans by New African magazine.

"I hope to continue to develop preclinical tools that will facilitate prioritization of small molecules during their chemical (lead) optimization phase based on their predicted pharmacological profile in African patients."

JOHN CHIMINSKI

CHAIR AND CEO AT CATALENT

In the more than 20 years Chiminski has spent at Catalent, he has overseen the company's strategy to help accelerate the small molecule development process and improve clinical outcomes. "We want to power the innovation and growth of the life science industry by becoming its leading development and commercial partner. To do that, we have built our team and capabilities to be in the best position to help innovators with development expertise, delivery technologies, and the right-scale manufacturing platforms to bring more of these programs to patients."

PAOLO COLOMBO

EMERITUS PROFESSOR AT THE UNIVERSITY OF PARMA

Colombo joined the University of Parma, Italy, in 1986. His interest in drug delivery research focuses on oral, transdermal, and inhalation products. He has patented over 40 different drug delivery systems, many of which have become registered products. He is also the Chief Executive Officer of PlumeStars and Fellow of AAPS, AIMBE, and CRS. "My personal opinion is that the lesson of COVID-19 has to be capitalized on and not forgotten, because similar diseases and pandemic situations, coming from our global lifestyle, could be repeated."

WILL DOWNIE

CEO AT VECTURA

Downie has over 30 years of industry experience and joined Vectura as CEO in November 2019 – helping the company implement its strategic change from an inhaled therapy development company to CDMO in the inhalation field. When asked to comment on the impact of COVID-19 on pharma, he responded, "Often, out of a crisis, great things happen. This is clearly a moment in time where the world has faced one of its biggest challenges, with the pharma industry playing a central role in fighting the pandemic. I truly believe we will look back on COVID-19 as a seminal moment – a time where the impossible was made possible."

ATHENA COUNTOURIOTIS

PRESIDENT AND CEO AT TURNING POINT THERAPEUTICS

Countouriotis' experience includes large and small molecule therapeutics in hematologic and solid tumor indications, with multiple regulatory approvals in the US and Europe. In 2018, Countouriotis joined Turning Point Therapeutics' board of directors and also became the company's President and Chief Executive Officer. She also serves on the board of directors of Iovance Biotherapeutics and Passage Bio.

"The speedy development of COVID-19 vaccines may provide a template for some drug development projects. Though that approach won't apply in all settings, 'speed' is an attribute we value and recognize at Turning Point. We see it as our duty to bring differentiated therapies to patients as rapidly as possible, which leads us to think creatively and collaboratively with regulatory agencies about important topics like trial design."

EDWARD HAEGGSTRÖM

CEO AT NANOFORM

In 2015, Haeggström commercialized the nanoparticle engineering platform he developed with Jouko Yliruusi, Acting Professor at the University of Helsinki, Finland. This marked the beginning of Nanoform. Haeggström is also a professor at Helsinki University and Head of the Electronics Research Laboratory within the Department of Physics. When asked about his future aims, he responded, "My ambition is to continue pushing the progress of nanoparticle engineering on a global scale. By furthering the reach of our small molecule and biologics nanoforming technologies, we can provide promising therapies with a route to market and improve existing therapies."

ALISON HOLMES

PROFESSOR OF INFECTIOUS DISEASES AT IMPERIAL COLLEGE LONDON

Holmes is also a Fellow of the Academy of Medical Sciences and an NIHR Senior Investigator. She leads a multidisciplinary research group and collaborates with international organizations to help improve the pharmaceutical industry's response to antibiotic-resistant infections. She is also the President of the International Society for Infectious Diseases – a body established to support a range of stakeholders in the management and prevention of infectious disease outbreaks.

NIK KOTECHA

CHAIRMAN OF MORNINGSIDE PHARMACEUTICALS LTD

A self-made entrepreneur, Kotecha established generic medicines manufacturer and supplier Morningside Pharmaceuticals from a home garage in the 1990s. Since then, Morningside has grown to be one of the leading UK suppliers of a wide range of quality generic medicines to international aid organizations, having exported to more than 120 countries worldwide since its inception.

Outside of Morningside, Kotecha regularly advises businesses and government departments. He is a Department for International Trade (DIT) Export Champion, a CBI Regional Councillor, and a Board Member for the British Generic Manufacturers Association (BGMA). In 2017, Kotecha set up the Randal Charitable Foundation, which works to ensure that grants reach charities helping individual people in need of assistance and has directly led to more than 145,000 lives being saved so far.

JOHANNES KHINAST

PROFESSOR OF PHARMACEUTICAL ENGINEERING AT GRAZ UNIVERSITY OF TECHNOLOGY AND CEO AT RCPE

Khinast has almost 300 publications in refereed journals and 10 patents registered under his name, and has worked with numerous pharmaceutical companies as an advisor for the implementation of novel drug formulations. "Pharma will look back on COVID-19 as a game-changer that hopefully brought back API production to Europe. We will be better prepared to face another health crisis in the future by reacting faster and making rapidly invented drugs accessible for a large number of people around the world."

M. N. V. RAVI KUMAR

PROFESSOR AT THE UNIVERSITY OF ALABAMA IN TUSCALOOSA

Kumar's lab develops non-competitive receptor targeting carrier systems for oral drug delivery applications in human health and disease. Their rational design of biodegradable polyesters with tunable ligand-receptor stoichiometry has enabled the clinical translation of small molecule drugs with otherwise poor oral bioavailability. "I am confident that our technologies will not only facilitate drug repurposing, but also minimize attrition rates when applied early in drug discovery programs. The majority of human conditions remain safely, efficaciously, and economically managed with traditional pharmaceuticals, especially when novel formulations are considered. Small molecule drugs remain a central plank of academic-industry innovation and are here to stay."

ANDREW MOORE

GENERAL MANAGER AT PFIZER CENTREONE

Moore joined Pfizer CentreOne during the COVID-19 pandemic. But with over 18 years of leadership experience, Moore was unphased by the change. He says, "The pharmaceutical industry will look back at this historic period as the catalyst that propelled us to do things differently and collaborate in ways not seen before. We found ways to be more innovative because we worked closely together to find solutions faster and overcome challenges at a time of unprecedented need. This was often achieved despite working remotely and conducting meetings virtually. There are many lessons learned throughout this experience, some of which we haven't even realized today."

ROBERT S. LANGER

DAVID H. KOCH INSTITUTE PROFESSOR AT THE MASSACHUSETTS INSTITUTE OF TECHNOLOGY

Arguably one of the most prolific inventors in all of medicine and with over 1,300 issued and pending patents, Langer's work has impacted many lives. He holds 34 honorary doctorates and has been elected to the National Academy of Medicine, the National Academy of Engineering, the National Academy of Sciences, and the National Academy of Inventors. He has also served on the FDA's Science Board from 1999 to 2002.

NIGEL LANGLEY

GLOBAL TECHNOLOGY DIRECTOR AT BASF

Langley has written over 100 scientific publications and co-edited two books. He is also an adjunct professor at the University of Mississippi and a Fellow of the UK's Royal Society of Chemistry. In 2018, he was awarded the Industry Research Achievement Award in Excipient Technology by the IPEC Foundation. He has been a member of the Executive Committee at IPEC Americas since 2010 and is currently Chair Elect. He is also helping to lead the Novel Excipients Initiative for IPEC Americas in collaboration with the IQ Pharma Consortium. "I have a passion and interest in innovation especially in the area of pharmaceutical excipients. I am hopeful that, in the coming years, excipient innovation will become a key driver in the pharmaceutical industry, in both biologics and small molecule drug development. Without the opportunity to develop new excipients that have been specifically designed to help address current and future formulation challenges – for example, in improving the stability of biologics and in the area of poorly soluble small molecules – these challenges will remain unmet and, as a consequence, optimal medicines will not be available to the patient."

FAITH OSIER

GROUP LEADER, MALARIA VACCINE DEVELOPMENT AT KEMRI – WELLCOME, KENYA AND VISITING PROFESSOR OF IMMUNOLOGY AT OXFORD UNIVERSITY

Osier's work focuses primarily on the eradication of malaria and is currently exploring the possibility of developing a vaccine against the disease. She is also the President of the International Union of Immunological Societies, and oversees the FAIS Legacy Project, which aims to train 1000 African immunologists over 10 years.

G.V. PRASAD

CO-CHAIRMAN AND MANAGING DIRECTOR AT DR. REDDY'S LABORATORIES

Prasad has played a key role in Dr. Reddy's operations since the company's inception. A firm believer in sustainable manufacturing, he leads initiatives on the adoption of green technologies and processes. Most recently, he was declared a Regional Honoree for the 2020 YPO Global Impact Award, was conferred the V. Krishnamurthy Award for Excellence by the Centre for Organizational Development in 2019, and received The Boundary Breaker at the CEO Awards in 2018.

JOHN TALLEY

CHIEF SCIENTIFIC OFFICER AT EUCLISES PHARMACEUTICALS

Talley joined Euclises Pharmaceuticals in 2011 and has co-invented several marketed drugs. He also serves as Partner and Vice President-Chemistry at Emmyon, advising on the identification of new chemical entities. "My ambition in the near future is to continue to be actively engaged in drug discovery research programs. I would love to have access to laboratory facilities for hands-on experimental research because I thoroughly enjoy it."

MATTHEW TODD

PROFESSOR OF DRUG DISCOVERY AT UNIVERSITY COLLEGE LONDON

Todd founded and currently leads various open-source drug discovery consortia, including Open Source Malaria, Open Source Antibiotics, and MycetOS. These focus on ways that open science can accelerate the discovery of new medicines: all data and ideas are freely shared, anyone may participate, and there are no patents. His research interests span drug discovery and the development of new synthetic methods.

"Small molecules can be tremendously powerful, effective, safe, inexpensive, and (because of their simplicity) 'democratisable' in that lots of laboratories can be involved in their optimization. We need every weapon available if we are to combat disease more effectively."

MARTIN VAN TRIESTE

PRESIDENT AND CEO AT CIVICA RX

Under Van Trieste's leadership, Civica has expanded its membership to include more than 50 health systems across the US and has delivered more than 40 essential medications for hospitals, 11 of which are being used to treat COVID-19 patients. Most recently, Civica began providing its medicines to the US Department of Veterans Affairs and the US Department of Defense. During the peak of COVID-19 outbreaks in the US, Van Trieste led efforts to deliver 2.1 million containers of Civica medicines to the country's Strategic National Stockpile.

"It was satisfying to see how the pharmaceutical industry responded quickly, collaboratively and effectively in response to COVID-19 – and improved our reputation, which has been damaged in recent years. We are in the biotechnology century. We will look back and say we learned more about human biology, how our DNA impacts the effectiveness of treatments, and how we can design drugs to target a specific disease. As a result, we will all benefit from cures and not just treatments for chronic conditions."

Top 20

HAL BASEMAN

CHIEF OPERATING OFFICER AT VALSOURCE

"The global pandemic has resulted in the need to accelerate the development, approval, and distribution of COVID-19 related products. This need, combined with the complexities of manufacturing drug products during a time of pandemic related-restrictions, has uncovered areas where there are opportunities for improvement. This includes: risk- and science-based regulatory decision making to help companies and regulators prioritize and evaluate alternative and better means to control drug manufacturing processes; manufacturing supply reliability to ensure essential materials are available; expansion of capability to provide production lines for the manufacture of essential drug products; technical resources to develop and implement drug product manufacturing methods and technologies; and harmonization, modernization, and understanding of post-approval change procedures and requirements to provide the most valuable information needed for the expansion of drug product manufacturing output and reduce barriers to that expansion."

KAREN FLYNN

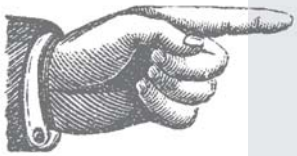
PRESIDENT, BIOLOGICS & CHIEF COMMERCIAL OFFICER AT CATALENT

Prior to joining Catalent, Flynn served as the Senior Vice President and Chief Commercial Officer of West Pharmaceutical Services. "One of the lessons learned from the pandemic is that the partnerships between public and private entities, spanning academia, government, and non-profit organizations, and even between companies that would traditionally compete, have been hugely beneficial in getting vaccines and therapies to patients as quickly as possible. This unprecedented sharing of knowledge has paved the way to find solutions."

RICK BRIGHT

SENIOR VICE PRESIDENT, PANDEMIC PREVENTION & RESPONSE, HEALTH INITIATIVE AT THE ROCKEFELLER FOUNDATION

Bright joined The Rockefeller Foundation in March 2021 to lead the development of the Foundation's pandemic data and action platform, which will help prevent future pandemics by identifying and responding to the earliest alerts of a disease outbreak and stopping it in the first 100 days. He has extensive experience in global public health and most recently served the US Department of Health and Human Services as the Deputy Assistant Secretary for Preparedness and Response, and Director of the esteemed Biomedical Advanced Research and Development Authority (BARDA). Bright resigned from government service in protest against the Trump administration's approach to handling the COVID-19 pandemic, specifically over the level of political interference in science and the spread of inaccurate information that he said was "dangerous, reckless and causing lives to be lost."



KENNETH C. FRAZIER

CHAIRMAN OF THE BOARD AND CEO AT MERCK SHARP & DOHME

Frazier started out as a lawyer and has taught trial advocacy in South Africa. He joined MSD's public affairs division as a general counsel in 1992, and became CEO in 2011. He will retire from the role of CEO as of June 30, 2021, but will continue to serve as an executive chairman on the board of directions for a transition period. "It has been a privilege to serve as Merck's CEO for the past decade and to work with the most dedicated and talented employees and management team in the industry," Frazier said in a company statement.

JUSTIN HANES

LEWIS J. ORT PROFESSOR OF OPHTHALMOLOGY AT JOHN HOPKINS UNIVERSITY; AND DIRECTOR AT THE CENTER FOR NANOMEDICINE

"The most defining moments of my career involve the many people who have influenced my thinking, and with whom I have worked to create new methods to make drugs safer and more effective. Big problems are rarely solved by individuals. Thus, my most defining moments include: meeting my mentors, including Robert Langer of MIT, and Henry Brem and Drew Pardoll of Johns Hopkins; the opportunity to work with scores of amazing students, postdoctoral fellows, and colleagues at Johns Hopkins; the vision of the Wilmer Eye Institute led by Peter J. McDonnell to start a center of excellence focused on the intersection of medicine and nanotechnology, and being asked to be its founding director; and support from the generous philanthropists and investors who have catalyzed our discoveries, allowed many of them to be tested in human clinical trials, and helped maximize the good our inventions can do for humanity."

JACKIE HUNTER

BOARD DIRECTOR AT BENEVOLENTAI

Hunter has over thirty years of experience in the bioscience research sector, working across academia and industry, including leading neurology and gastrointestinal drug discovery and early clinical development for GlaxoSmithKline.

"BenevolentAI leverages machine learning to help scientists view and reason across all of the world's available biomedical information to solve complex drug discovery challenges. Last year, the company identified baricitinib as a treatment for COVID-19, which later won FDA approval for use in hospitalized patients. Post-pandemic, we should expect industry conversations to revolve around how we use AI to improve future health systems and revolutionize the drug discovery process. Another topic that will dominate the industry post-COVID is how we improve and unblock approval processes for future therapies and vaccines. We have seen how approvals can be expedited with rolling data reviews and large data trials in the pandemic, and, as a result, we have witnessed huge scientific leaps in vaccine development."

MAIK JORNITZ

PRESIDENT AND CEO AT G-CON MANUFACTURING

"For me, it is always exciting and encouraging to see new therapies being developed, especially fighting against cancer, but nowadays also rare diseases, which had no treatment options in the past. Treatments against cancers are now becoming a targeted approach, instead of affecting the patient's entire body. In other cases, patients who had no chance of survival now see hope that their disease may be treated. These inspiring treatment steps forward make me want to work harder to find the manufacturing and process solutions to support such efforts. The COVID-19 pandemic and the incredible speed at which vaccines have been developed highlight an urgency for much-needed solutions. We as an industry have come a long way for the better of the patient – and I find this very motivating."

MARIA JOSÉ ALONSO

PROFESSOR AT THE UNIVERSITY OF SANTIAGO DE COMPOSTELA CIMUS RESEARCH INSTITUTE

Alonso's lab has pioneered numerous discoveries in nanomedicines and she is also a past president of the Controlled Release Society. She has coordinated research consortia financed by the WHO, the Gates Foundation, and the European Commission, and is the author of almost 300 scientific contributions. For Alonso, biotechnology, nanotechnology, and artificial intelligence will drive the future of the pharma industry.

JEAN-PAUL KRESS

CEO AT MORPHOSYS

"One lesson from COVID-19 is the idea that scientists in industry, academia, and government can coordinate activities better and work more openly together to rapidly develop transformational medicines in the future. Such collaborations should have impacts far beyond pandemics to provide patients with better treatments for life-threatening diseases such as cancer. At MorphoSys, we've learned that including innovative clinical strategies with real-world evidence studies and pursuing accelerated pathways for breakthrough medicines can lead to accelerated drug development and approval."

Since joining MorphoSys as CEO in September 2019, Kress has strategically repositioned the company from an antibody technology provider to a commercial-stage biopharma company.

EMMANUEL LIGNER

PRESIDENT AND CEO AT CYTIVA; GROUP EXECUTIVE AT DANAHER BIOTECHNOLOGY GROUP

Ligner has been the President and CEO of Cytiva since July 2017, when it was known as GE Healthcare Life Sciences.

"I'm excited about the development of new modalities. It's amazing to see years of research and development come to fruition with mRNA technologies and cell therapies finally reaching patients. We must continue investing in automation and digital technologies that will help accelerate the development and manufacture of these novel therapeutics, so we can reach as many patients as possible."

NEIL KUMAR

FOUNDER AND CEO AT BRIDGEBIO PHARMA

Prior to founding BridgeBio in 2015, Kumar served as a principal at Third Rock Ventures, the interim vice president of business development at MyoKardia, and an associate principal at McKinsey & Company. "What are the most exciting technologies that will drive the future of pharma? There are so many! To start, technologies that help us better interrogate genetics and link DNA sequence to RNA transcription and protein translation, through more sensitive transcriptomics (single cell and bulk) and quantitative mass spectrometry proteomics. Second, we have more and better quality datasets of human mutations which help us identify new, causal pathogenic variants in different populations. Third, we have made rapid progress on technologies like cryo-EM and CRISPR screens to understand the effect of mutations on protein structure, cellular function and systems dysregulation. The confluence of these technologies promises better medicines to patients faster in the future."

RINO RAPPUOLI

CHIEF SCIENTIST AND HEAD OF EXTERNAL R&D AT GLAXOSMITHKLINE

Considered one of the world's leading vaccine experts, Rappuoli was involved in the development of CRM197 used in H. influenzae, N. meningitidis, and pneumococcus vaccines, and has introduced several novel scientific concepts. He is also actively involved in research and development. Rappuoli and a team of Italian scientists at the Monoclonal Antibody Discovery Lab have been conducting extensive work on SARS-CoV-2 and recently demonstrated three mutations that allow the virus to evade the polyclonal antibody response of highly neutralizing convalescent plasma.

MIKE REA

CEO AT IDEA PHARMA

Rea is building off the applied innovation platform of IDEA and the lessons of the Pharmaceutical Invention and Innovation Index to launch Protodigm – an alternative research organization that brings a constellation of technology to the ODE (options, decisions, evidence) challenge to deliver disruptive development approaches.

"There is so much amazing technology that could support pharma that is not reaching into development because companies are stuck on what worked last year versus what could work next year. One huge area is drug delivery – from what is druggable, to what is soluble, to how it can be delivered to its target. So much can be unlocked by thinking differently early."

KIRAN MAZUMDAR-SHAW

EXECUTIVE CHAIRPERSON AT BIOCON AND BIOCON BIOLOGICS

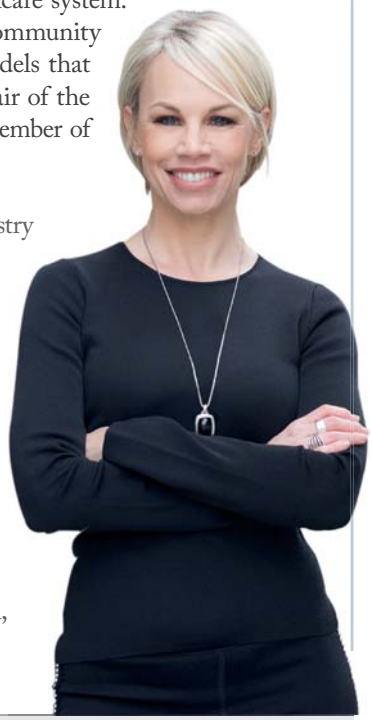
Mazumdar-Shaw is seen as a pioneering biotech entrepreneur, a healthcare visionary, a global influencer, and a philanthropist. She is the recipient of two of India's highest civilian honours: the Padma Shri and Padma Bhushan. She has also received many other accolades from overseas. She serves on the board of MIT, Pure-Tech Health, Infosys, and Narayana Health, and holds key positions in various industry, educational, government, and professional bodies globally.

"A positive outcome of the pandemic is the global commitment to collective surveillance and pandemic prevention and preparedness. At long last, healthcare investment is likely to see a sharp increase across the world. Moreover, the crisis has brought to the fore a host of complex issues around drug pricing and distribution, as well as a number of social and other inequalities that are now demanding close attention."

MELINDA RICHTER

GLOBAL HEAD OF JLABS AT JOHNSON & JOHNSON INNOVATION

Before joining JLABS, Richter was the Founder and CEO of Prescience International, which was dedicated to accelerating research to the patient. Richter created the company after a medical emergency left her questioning the efficiency of the current healthcare system. In her current role, she supports the innovation community by creating capital-efficient commercialization models that help early-stage companies. She is also Board Chair of the California Life Sciences Association and a board member of BIO's Technology Transfer Committee.



"COVID-19 accelerated trends in the healthcare industry which have and will continue to create more value for everyone. We've seen parallel processing in drug development accelerate time to market for life-enhancing, life-saving therapies; collaboration across companies, borders, and types of organizations to meet an urgent health security threat; an increased focus on health equity and diverse clinical trials to bring more potential solutions to people who've had marginalized care; and more options to get and cover virtual care outside of traditional institutional offerings. I feel the crisis of COVID-19 demanded creativity, generosity, empathy and pure determination, and each of us played our part."

GIL ROTH

PRESIDENT AT THE PHARMA & BIOPHARMA OUTSOURCING ASSOCIATION

Roth founded PBOA in 2014 to give a voice to the CDMO sector in regulatory, legislative and business matters. During the pandemic, he helped connect the federal government and other parties with CDMOs to develop and manufacture treatments and vaccines. Alongside his work with the pharma industry, he also runs a cultural podcast called The Virtual Memories Show.

"Post-pandemic, the industry – and governments across the world – will have to answer major questions about pharma supply chains. Our members have risen to the challenge of helping develop and manufacture vaccines and therapeutics for COVID-19 while maintaining supply of their clients' non-COVID products, but it remains to be seen how manufacturing infrastructure will change to accommodate the potential for more global vaccination programs."

JAMES N. THOMAS

EVP, GLOBAL HEAD OF BIOTHERAPEUTICS AND PRESIDENT OF US OPERATIONS AT JUST - EVOTEC BIOLOGICS

Over the course of his career, Thomas has contributed to the advancement of many important therapeutics including Activase, Vectibix, Enbrel, Prolia/Xgeva, and Repatha, as well as numerous biosimilar programs. Thomas is passionate about creating and using innovative technologies to meet the needs of patients. In 2014, he co-founded and became CEO of Just Biotherapeutics, with a focus on expanding global access to biologics, and is now continuing this journey at Just - Evotec Biologics.

"How can we accelerate drug development projects of the future? Through systematic, vertically integrated modality platforms bound together and defined through a common data pool. Acceleration requires prediction, and the machine learning and AI tools that are available or emerging will be capable of doing this if the right data are captured and registered. A data-rich systems approach should go as far back into the discovery process as possible to capture improvements to speed, cost, quality, number of clinical experiments and ultimately clinical success rates. This approach will not only accelerate drug development, but reduce R&D costs and, ultimately, improve patient access."

JAN VAN DE WINKEL

PRESIDENT AND CEO AT GENMAB

After co-founding Genmab and serving as President, Research and Development and Chief Scientific Officer, van de Winkel was appointed President and Chief Executive Officer in 2010. Under his leadership, Genmab has created three antibody medicines that all received Breakthrough Therapy Designations from the FDA and are now commercialized by partners: Darzalex, a backbone therapy for multiple myeloma, commercialized by Janssen; Kesimpta by Novartis; and Tepezza by Horizon Therapeutics.

"We believe that partnerships and collaborations are foundational to accelerate innovation and bring medicines to patients as quickly as possible. It takes an innovation ecosystem with partnerships between biotech and big pharma, academia, research institutes, data sciences companies or medical electronics companies to catalyze break-through innovation."

MIKE VANDIVER

SENIOR VICE PRESIDENT OF BIOTHERAPEUTIC OPERATIONS AT JUST - EVOTEC BIOLOGICS

Vandiver has over 30 years of biopharmaceutical process development and manufacturing experience. At Just Biotherapeutics, he led efforts to bring the company's clinical GMP facility, online. Now at Just - Evotec Biologics, Vandiver is leading efforts to bring the company's first North American J.POD clinical and commercial biomanufacturing facility online. When considering the most exciting technologies that will drive the future of the industry, Vandiver says: "Deployable and portable biologics manufacturing is gaining more momentum as a result of the pandemic. Assurance of regional supply and rapid response will fuel further development of the enabling technologies. This future may be closer than we think."

EMMA WALMSLEY

CEO AT GLAXOSMITHKLINE

Walmsley first joined GSK in 2010, initially working for the Consumer Healthcare, Europe, division. She became CEO in April 2017. The company missed a key internal profit goal in 2020 due to the impact of the pandemic, but still performed well. Recently, the company announced promising results from a phase III trial with Vir Biotechnology for a monoclonal antibody to treat COVID-19.

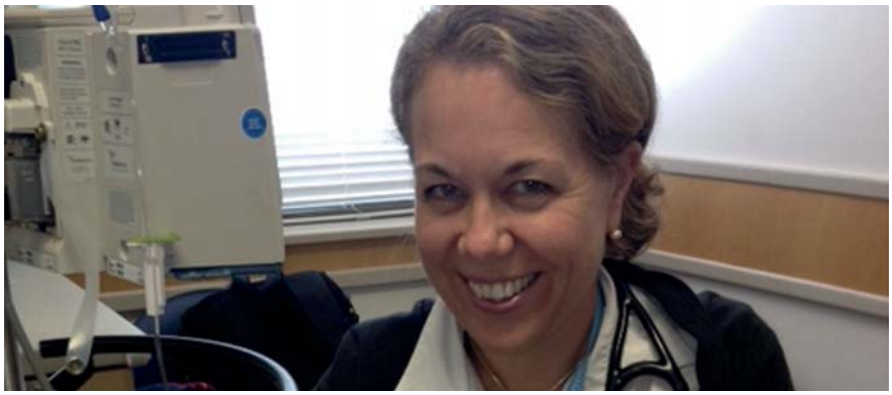
ADVANCED MEDICINE

Top 20

USMAN "OZ" AZAM

PRESIDENT AND CEO AT TMUNITY THERAPEUTICS

As head of cell and gene therapy at Novartis between 2014 and 2016, Azam was part of the team that brought the first CAR T cell therapy to market. Before that, he held various science, regulatory and commercial roles at Aspreva, J&J and GSK, but originally trained as an obstetrician and gynecologist. At Tmunity, Azam is focused on bringing the next-generation of T cell therapies to market. He is also on the board of directors for the Alliance for Regenerative Medicine.



CATHERINE BOLLARD

DIRECTOR AT THE CHILDREN'S NATIONAL RESEARCH INSTITUTE; AND PROFESSOR OF PEDIATRICS AT GEORGE WASHINGTON UNIVERSITY

"The success of the mRNA vaccine technology for COVID-19, I believe, has huge implications for the cancer vaccine field and, ultimately, for combination vaccine and cell therapy approaches for cancer and virus infections. But the biggest challenge remains the centralized manufacturing model for large-scale patient-specific products as more cell therapies are getting approval (for example, the latest approval of the Bristol Myers Squibb BCMA-CAR T cell product for myeloma). Looking to the future, cell-based therapies will not be sustainable with a purely patient-specific centralized manufacturing model and, therefore, the field must move into the development of off-the-shelf cell therapies. The success of off-the-shelf virus-specific T cells is especially exciting because it has the potential to be the platform for other antigen specific and CAR T cell therapies."

VERED CAPLAN

CEO AT ORGENESIS

Orgenesis recently announced several collaborations with international institutions, including Johns Hopkins University and the University of California, Davis, both of which joined the company's POCare network. Caplan says, "We as an industry must invest in building the frameworks that will allow scientists to translate their advancements to industrial products. It's not enough to make these therapies available, we must make them available for all that need them."

She likens the industry to the early days of computers. "We are building more sophisticated hardware (cell and gene processing systems) that in turn drives more software development (the molecular biological pathways by which we manipulate cellular systems) that again requires more advanced hardware. We can only imagine what the future holds."

JENNIFER DOUDNA

LI KA SHING CHANCELLOR'S PROFESSOR OF BIOMEDICAL SCIENCE AT UNIVERSITY OF CALIFORNIA, BERKELEY

Along with Emmanuelle Charpentier, a Director at the Max Planck Institute for Infection Biology in Berlin, Doudna played an instrumental role in the development of CRISPR-Cas9. The pair were the first to suggest that the technology could be used for gene editing. For her contribution to the cell and gene field, Doudna was the co-winner of the 2020 Nobel Prize for chemistry. Her current research focuses on RNA-guided gene regulation.

MASSIMO DOMINICI

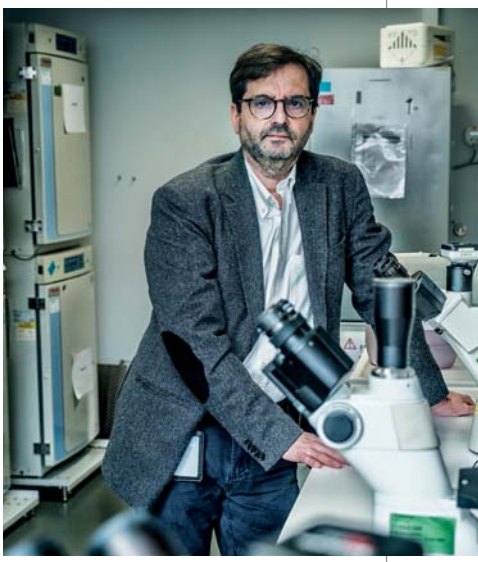
PROFESSOR AT THE UNIVERSITY HOSPITAL OF MODENA AND REGGIO EMILIA; AND SCIENTIFIC FOUNDER OF RIGENERAND

"COVID-19 has led to challenges with clinical trials; almost 1500 trials have reported delays due to the pandemic. This is particularly true for phase I studies. For those, almost half of the trials that have been delayed have had a special impact in oncology. Considering that cell and gene therapies have their big fraction of investigations in that phase, this could have a relevant impact on the field. The big challenge – but also opportunity – for the industry is how to adapt to the current and possibly enduring situation and how to conceive new ways to conduct trials, accounting for regulatory frameworks, new technologies, and new needs."

FABIAN GERLINGHAUS

CO-FOUNDER AND CEO AT CELLARES

"The biggest challenge commercial cell therapy developers are facing is their inability to scale manufacturing to meet patient demand. The one-dose-at-a-time approach is highly labor-intensive, failure prone, and extremely difficult to scale with manual methods. For example, to produce 10,000 patient doses, one needs to run 10,000 separate manufacturing processes – each of which takes weeks and includes around 50 manual processing steps and 80 hours of touch time. This is a logistical nightmare; even the most pioneering companies in the cell therapy field struggle to treat a few thousand patients per year because of the lack of scalable manufacturing technologies. But I'm most excited about the creation of true end-to-end automation of cell therapy manufacturing platforms as they'll help accelerate access to life-saving cell therapies by resolving this manufacturing bottleneck. At Cellares, we believe the industry must move beyond 'semi-automated' processes, and toward the adoption of true automation. This is critical to de-risking the manufacturing process, reducing costs, and the risk of manufacturing failures, enabling cell therapy companies to treat significantly larger patient populations."



MIGUEL FORTE

CEO AT BONE THERAPEUTICS

"The development of vaccines for COVID-19 came about at lighting speed because of the alignment of a global need, regulatory support, and political will. Extensive scientific collaboration and focus to address a significant unmet medical need is an important lesson to extrapolate to the field of cell and gene therapies, where it is key to collaborate and combine emerging technologies to deliver what we know is bringing enormous value to patients with still unmanageable conditions."

Forte believes the main challenge for the industry in 2021 is access. "The field explodes with enabling technologies but the objective should always be to deliver the value to patients."

He is also excited about the increasing "professionalization" of biology: "Instead of cells learning 'on the job,' they will be administered already primed for tolerance, allogenicity, and for optimization of the therapeutic effect."

RACHEL HAURWITZ

PRESIDENT AND CEO AT CARIBOU BIOSCIENCES

Haurwitz co-founded Caribou Biosciences in 2011 with Nobel Prize winner Jennifer Doudna and other CRISPR scientists. Caribou is a clinical-stage company developing an internal pipeline of off-the-shelf genome-edited CAR-T and CAR-NK cell therapies for oncology. In 2014, she was named by Forbes Magazine to the "30 Under 30" list in Science and Healthcare, and in 2016, Fortune Magazine added her to the "40 Under 40" list of the most influential young people in business. In 2018, the Association for Women in Science recognized Haurwitz with the annual Next Generation Award. She also serves on the board of directors of the Biotechnology Organization (BIO).

DENG HONGKUI

CHANGJIANG PROFESSOR, THE BOYA CHAIR PROFESSOR, AND DIRECTOR OF THE INSTITUTE OF STEM CELL RESEARCH AT PEKING UNIVERSITY

In 1989, Hongkui left China for the US, working on HIV at New York University before switching to stem cells – eventually becoming research director of the stem cell company ViaCell in Cambridge, Massachusetts. He then went back to China after being awarded the prestigious Changjiang Professorship. In 2017, he and Chen Hu engineered resistance to HIV in mice using CRISPR gene editing, and for the first time used the technique on an AIDS patient – demonstrating the safety of CRISPR for humans.

BRUCE LEVINE

BARBARA AND EDWARD NETTER PROFESSOR IN CANCER GENE THERAPY AT THE UNIVERSITY OF PENNSYLVANIA

Levine believes the success of COVID-19 vaccine development carries lessons for cell and gene therapy by validating the benefit of long-term investment in research. "Additionally, the importance of a robust supply chain has gained wide acceptance during mass vaccination campaigns," he says. "In particular, the investment and knowledge gained implementing large scale cold chain logistics will carry lasting benefits for future delivery of cell and gene therapies."

Levine is looking forward to improvements both in viral vector manufacturing, and viral-free methods of gene delivery. "We will continue to see the implementation of multicomponent genetic engineering strategies to enhance cell function. As a positive ripple effect of the pandemic and the lipid nanoparticles and RNA breakthroughs, look for gene delivery and combination vaccine strategies with advanced cell and gene therapies."

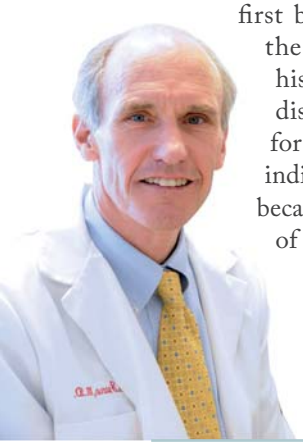
QUEENIE JANG

CEO AT ISCT

"Specialized training and development to populate the highly skilled cell and gene therapy workforce remains an essential task to enable the continued growth of the sector. Despite the pandemic, cell and gene companies raised almost $20 billion in 2020, more than doubling the amount raised in 2019 (according to the ARM State of the Industry, Jan 2021). There will continue to be huge demand for a skilled and qualified workforce to develop and deliver these therapies, requiring strategic investment from all stakeholders in the sector."

CARL H. JUNE

RICHARD W. VAGUE PROFESSOR IN IMMUNOTHERAPY AT THE UNIVERSITY OF PENNSYLVANIA



June is credited for the development of CART T therapy, which he first began to work on in the late 1980s. Today, his research involves the discovery of new CARs for a variety of disease indications. In 2020, June became an elected member of both the American Philosophical Society and the National Academy of Sciences.

PETER MARKS

DIRECTOR AT THE FDA CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

Over the past 12 months, Marks has played a pivotal role at the FDA in ensuring that COVID-19 vaccines are both safe and effective. Weighing in on how the pandemic may impact cell and gene therapy, he says, "The holistic approach to product development, simultaneously focusing on manufacturing challenges and clinical development combined with increased sponsor-agency interactions could potentially propel cell and gene therapy product development forward more rapidly."

For the future, he is most excited about the application of genome editing with base editors or similar technologies to

the treatment of human disease, which he thinks could be a "game-changer," as well as the application of advanced manufacturing technologies to cell and gene therapy production.

MARC MARTINELL

CO-FOUNDER AND CEO AT MINORYX

Martinell co-founded Minoryx to provide therapeutic options to patients of orphan diseases with no alternatives. The company recently presented results from its phase II/III ADVANCE study, showing that leriglitazone reduced progression of cerebral lesions and myelopathy symptoms in adrenomyeloneuropathy patients. Martinell has previously worked for Crystax Pharmaceuticals and Oryzon Genomics, where he managed several research projects and led the team in charge of target selection, structural biology, computational chemistry, and hit ID through a fragment-based approach. According to Martinell, the biggest challenge the industry faces this year is uncertainty.

BENJAMIN L. OAKES

CO-FOUNDER PRESIDENT, AND CEO AT SCRIBE THERAPEUTICS

Oakes has contributed to over 25 publications and patent applications across synthetic biology, molecular engineering, CRISPR, and zinc finger-based genetic modification. He received a PhD in Molecular and Cellular Biology from the University of California, Berkeley, in 2017, where he worked in the Doudna Lab and Savage Lab developing CRISPR-Cas9 molecules with enhanced characteristics. Scribe Therapeutics was spun out of the Doudna lab in 2018.

AMY RONNEBERG

CEO AT BE THE MATCH

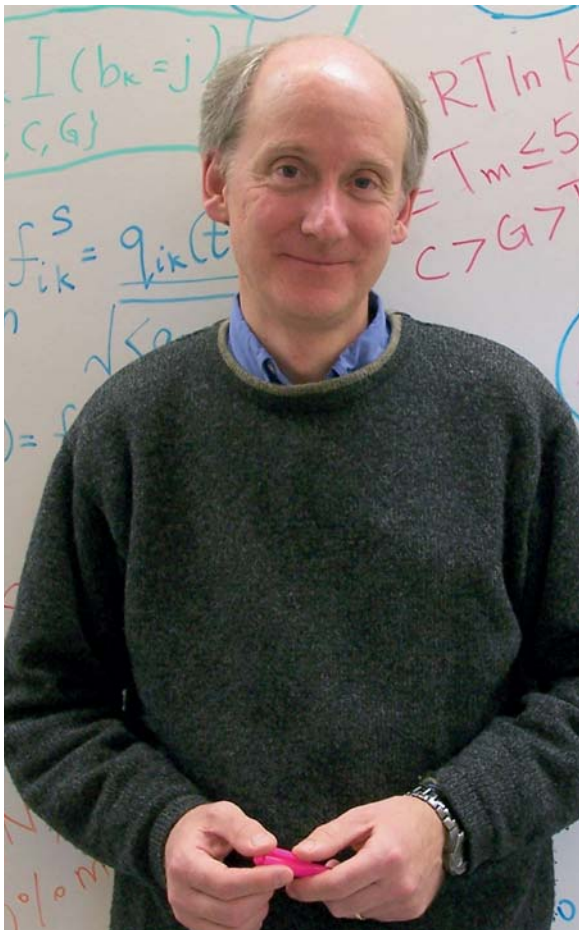
With an extensive history of leadership, Ronneburg has worked across a variety of sectors but joined Be The Match in 2013 as Chief Financial Officer. She assumed the position of Chief Executive Officer in 2020, and oversees more than 1,300 professionals and 3,000 volunteers who help manage the organization's stem cell registry for the development of novel cell therapies.

Around the same time that Ronneberg joined the company as CFO, she was diagnosed with cancer. She is now cancer free. In a statement, she said, "As a cancer survivor, I have personally felt what many other cancer patients and their loved ones encounter every day. My experience, the patients we serve, and our outstanding, dedicated employees are my motivation."

JAMES THOMSON

INVESTIGATOR, REGENERATIVE BIOLOGY AT THE MORGRIDGE INSTITUTE FOR RESEARCH AT THE UNIVERSITY OF WISCONSIN, MADISON

Thomson is a developmental biologist well known for his pioneering work isolating and culturing human embryonic stem cells in 1998, and developing human pluripotent stem cells from adult skin cells in 2007. In 2004, he founded Cellular Dynamics International to investigate the potential of human-induced pluripotent stem cells for drug discovery and toxicity testing. The company has since been acquired by Fujifilm. Thomson has been the recipient of many prizes and accolades during his career, including the King Faisal International Prize and the Albany Medical Center Prize in 2011.



EVELINA VÅGESJÖ

CO-FOUNDER AND CEO AT ILYA PHARMA

"The development of immunotherapies for oncology has been fantastic. I think the time is now for immunotherapies in other medical indications, steering the different immune cell subtypes to perform whatever tasks are needed – be it reducing fibrosis, increasing regeneration, fighting bacteria more efficiently, regulating blood pressure, or preserving organ function. With ILP-technology, we can use chemokines as therapeutics in a way that works well, is cost efficient, and has scalable manufacturing and a sustainable supply chain, by expressing them from lactic acid bacteria."

SHINYA YAMANAKA

DIRECTOR AND PROFESSOR AT THE CENTER FOR IPS CELL RESEARCH AND APPLICATION (CIRA); AND REPRESENTATIVE DIRECTOR OF THE CIRA FOUNDATION

Yamanaka is a world-renowned stem cell expert. He won the Nobel Prize in Physiology or Medicine in 2012 alongside John Gurdon for the discovery that mature cells can be converted to stem cells, but he has also won numerous other awards and prizes. Discovering the medical applications of induced pluripotent stem cells has been a major focus for Yamanaka since he first reprogrammed human cells in 2007. More recently, the CiRA Foundation has been involved in COVID-19 research by creating induced pluripotent stem cells from the blood of recovered COVID-19 patients and making them available to research institutions worldwide for free.

CLAUDIA ZYLBERBERG

CEO AT AKRON BIOTECH

"We've passed the eras of small molecules, chemistries, proteins (such as biologics and monoclonal antibodies) – now, it's nucleic acids' time to shine. By utilizing cellular machinery to redirect and recreate the destiny of our own cells, these powerful moieties can create more opportunities than ever in the therapeutic arena and beyond. A fascinating future is opening ahead of us. The global pandemic and worldwide pressure for a vaccine gave RNA the chance to show what it can do, if positioned properly. After years of trials around how to use this molecule in several applications, the opening came by way of COVID-19 vaccines. We have now expanded our toolbox and created a new therapeutic solution for complex problems in short timelines. With this comes growth in areas to support this new therapeutic modality (i.e., delivery systems and manufacturing schemes). Moreover, regulators globally were challenged to understand the value and opportunity to create solutions in a fast and efficient way without compromising safety. We gained lots of general knowledge about RNA and adenoviruses, and the global educational factor on these novel therapeutic vaccines will create a more open environment of acceptance for new remedies using RNA and DNA."

NextGen

R&D pipeline
New technology
Future trends

Raising the Bar(code)

Track and trace barcodes must appear on secondary packaging, but are here benefits to applying similar codes to parenteral containers?

By Stephanie Sutton

When thinking of traceability in the pharma industry, most of you will immediately think of serialization regulations, such as the Drug Supply Chain Security Act (DSCSA) or the EU Falsified Medicines Directive (FMD), which mandate the use of 2D matrix codes to be applied to each individual pack of pharmaceuticals (among other obligations). However, there is also room for traceability to be used in other ways to benefit pharmaceutical manufacturers. For example, applying unique product identifiers to glass containers could help prevent mix ups and allow manufacturers greater visibility into where problems are occurring in the fill and finish process.

The ISPE has published a Discussion Paper on the unique identification of primary containers to drive product traceability and quality (1). The paper outlines the current implementation of unique container identification technology in parenteral manufacturing lines, including potential solutions, and provides a summary of the challenges that technology developers face when it comes to developing and implementing identification solutions in process lines.

Tod Urquhart, Product Manager and Core Team Leader at Stevanato Group, has taken a lead role when it comes to drafting the paper. We spoke with him to learn more about the benefits of applying a unique identifier to glass containers.

Why did you become interested in the idea of unit-level traceability for glass containers?

There has been a lot of focus on pharmaceutical secondary packaging – and I think the industry breathed a huge sigh of relief when it met the mandates for the DSCSA and FMD. Compliance with traceability initiatives has cost companies hundreds of millions of euros/dollars. I have been working in serialization for well over a decade and I was interested in how we could take the concept of traceability further and deliver more value for the industry.

Most traceability solutions only apply to the secondary packaging. Once a product is removed from that packaging, the traceability is lost. Glass containers usually have a label on the container but it can still be damaged. Putting the finished product inside a secondary box is also the last step and provides no traceability on the manufacturing line. If a barcode were to be applied to glass pharmaceutical containers prior to fill-finish, it would allow tracking throughout the filling and sterilization processes, which could help identify problems or issues within the process, enable faster root cause analysis, and, ultimately, help companies improve their processes and save money.

Although adding a unique identifier to glass parenteral containers could offer many benefits for manufacturers, it is not easy to mark glass packaging. Glass is glossy and non-absorbent, and the containers also tend to be very small and have curved surfaces. In short, it is far more complicated than adding a barcode to secondary packaging of prescription medicines.

At Stevanato Group, we looked at the idea of marking containers with a laser solution, but it was rejected because the technology could potentially create micro-cracks in the glass. We looked at various other printing technologies – and someone told me that they had the need completely covered. But when I looked at their idea, it would have reduced our output per machine by around 50 percent. The industry would not want to absorb that cost – and we did not want to reduce our capacity so significantly. After that, we started to consider other technologies and looked at nine different solutions. In the discussion paper, several key characteristics are described for a marking process:

- It should be a digital process capable of managing high speed serial numbers and barcodes.
- Must have no impact on container integrity or glass mechanical properties.

- Must not be impacted by or impact on sterilization processes.
- Must have minimal impact on manufacturing lines (such as filling, inspection, etc.)
- Must be readable with standard serialization cameras.

How can manufacturers benefit from applying unique identifiers to parenteral containers?

In a PDA survey (cited in the ISPE discussion paper), respondents cited a variety of considerations that would inspire them to build a business case for implementing unit-level traceability of glass containers: limiting batch segregation, avoiding mix ups in the filling process, reject analysis inspection greater traceability in the event of a product recall, segregation of drugs in the market, automating reconciliation, racking, improving clinical trial monitoring, and increasing efficiency, such as overall equipment effectiveness.

I like to refer to unmarked glass containers as "vanilla glass." All the containers are identical and they move at high speed throughout the line. If there is a problem with, for example, particulates being present, the container will be rejected. However, when it is in the reject chute you do not know which container has been rejected for particulates, for example, or for a container closure integrity issue container without thoroughly examining the container and conducting an investigation. Unique container identification provides individual container visibility in the key manufacturing processes.

One challenge with filling lines is that batch release documentation may not be completed until two or three weeks after the product has been filled. If a problem is identified, manufacturers must ascertain the filled product that has been impacted and this is not an easy task. As such, it is common for manufacturers to over segregate or even write off the entire batch.

But if each container has a unique identifier there will be a date and time stamp associated with the point at which a container has been filled. If contamination is found, you can check the identity of the containers that were in the machine during the period of concern and use a defined segregation policy based on real data.

Once the batch is complete on a filling line, pharma companies must also ensure there is a complete reconciliation of the process, to prevent the potential for a mix up when a different filling process begins. The reconciliation process is laborious; if 100,000 containers go into the machine there must be a complete count to check that 100,000 containers came out! By marking individual containers, the whole process can be automated. You know exactly which containers entered the machine and once you know which containers have been rejected, you'll know if any containers are missing – and potentially still in the line.

Traceability gives individual container visibility in the line. You will know the date and time each container was filled, which pump was used, and how long it took – and

this insight could be used to improve the process overall. In the same way, unique containers can be used in the automated inspection process. Today, when a defect is detected it is difficult to determine the reason a container was rejected without additional manual intervention. Unit level traceability will indicate which container was rejected and why, thus helping with process improvement and reconciliation.

There are also benefits beyond manufacturing. Traceability is incredibly useful during a product recall. I was working at a pharmaceutical distribution company in Asia during a product recall, and that is when it really hit home how important serialization is. Keeping track of the status of the recall was very challenging. We had no idea where the affected products had gone. Which doctor, clinic, or pharmacy had them? Or were they already in somebody's medicines cabinet? It seemed an impossible task.

Filling	*Inspection*	*Packing*	*Distribution and drug delivery*
Limited segregation of quality issues	Reject cause tracking due to container production deviations	Ensuring each final pack contains the correct filled containers	Traceability in the case of a product recall
Mix-up avoidance of filled containers	Reject analysis by type to facilitate detailed root cause analysis	Association of containers to secondary pack	Segregation of problematic marketed drugs due to filled product
Reject cause tracking due to filling deviations			Segregation of problematic marketed drugs due to containers
Automate batch reconciliation			

Table 1: Benefits of unit-level traceability for glass containers

How did you get involved with the PDA and the ISPE?

In 2016, I went to a PDA meeting in Venice and started talking about the concept of unique identification for parenteral drug containers. At that time, it was not on anyone's radar and so understanding the concept and why it may be important was a challenge! But, in time, the PDA began to understand the potential benefits and they have been very supportive by conducting surveys of their members to get viewpoints on traceability. In one of their surveys, they asked if their members would consider using unique containers; 68 percent of respondents said yes, which was a ringing endorsement to what we were doing!

"One challenge with filling lines is that batch release documentation may not be completed until two or three weeks after the product has been filled."

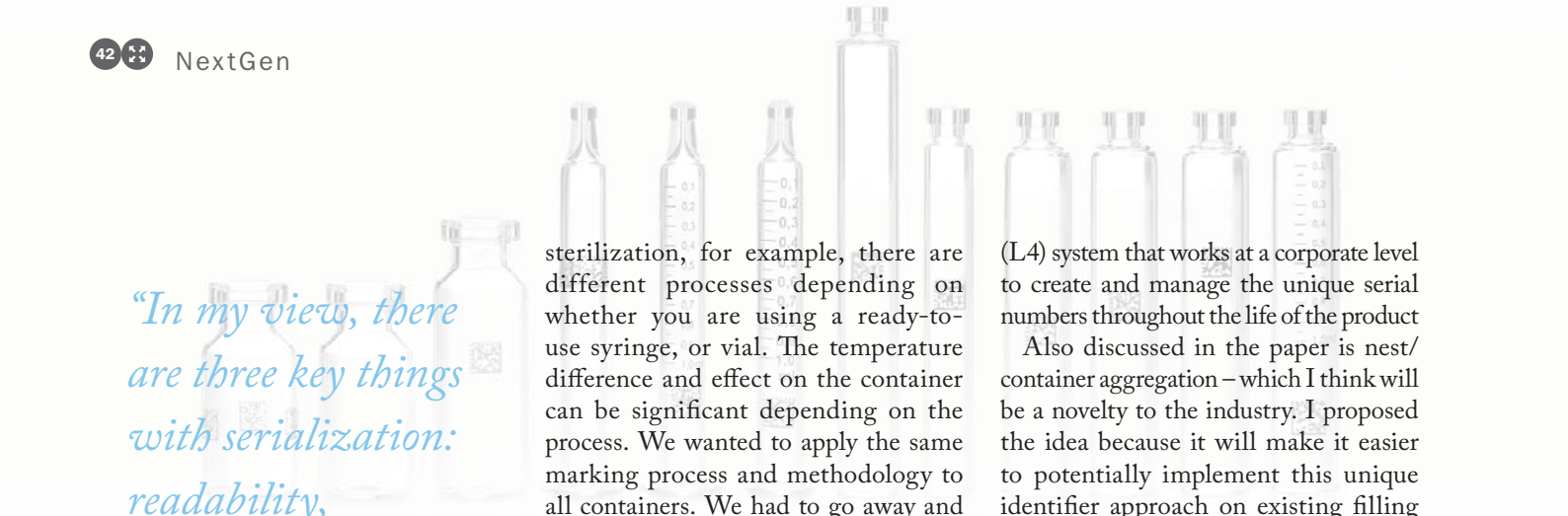
In 2019, I started looking at different standard agencies to see if they could offer support because the pharma industry is driven by standards! I went to a few different organizations. One of them told me that it would be much easier to get support if I was from a big pharma company; but, as I was from a supplier company, it may be more difficult!

But the ISPE stepped up and offered their support. They have been incredibly helpful. Other people showed their support too and we have authors on the discussion paper from many different companies, including LifeBee, Eli Lilly, Novartis, Groninger, Optima, Seidenader, Vetter, Alexion, Alfasigma, CIM Pharma, ISPE, and Janssen-Cilag.

I believe that the solution for unit-level traceability cannot just come from one supplier. Stevanato Group is not the only supplier to our customers – they will also be working with our competitors, as well as equipment providers. The challenge requires a multi-ended strategy and work from different parties to make it successful.

A working group was set up with the initial aim of creating a discussion document that could be used for implementing unique identification of primary glass containers. Because of the pandemic, nobody was traveling so we were able to have our weekly group meetings with everyone attending – and it allowed us to work quickly and consider the viewpoints of pharma manufacturers, filling line manufacturers, inspection machine manufacturers, and so on.

There is a lot of detail in the document, and it outlines how to go about implementation. The whole point of a



"In my view, there are three key things with serialization: readability, readability, and readability."

standard is to make something easy, not just for pharma manufacturers but also for suppliers like us. It is about creating a level playing field and understanding how we can all work together. From the very start, the aim has been to develop an open-source solution that can be used by the industry through a licensing model.

What were the considerations around where to place the barcode?

We had a lot of conversations about this in the working group. We did some tests using our process to test the best place for the barcodes in terms of readability and not creating defects in the container. When discussing 0.5 mL syringes, a group of engineers from one pharma company said that they did not want the code anywhere on the body because it would prevent the detection of particulates during inspection. They wanted the code on the plunger, but I strongly advised against that because it is the plunger that guarantees drug sterility during the shelf life. We eventually agreed it should be placed on the body. The discussion paper states the recommended place to apply the code, depending on whether you are using a syringe, cartridge, or vial.

How will the barcodes be applied in practice?

To answer this, I need to take a step back and look at the processes. For sterilization, for example, there are different processes depending on whether you are using a ready-to-use syringe, or vial. The temperature difference and effect on the container can be significant depending on the process. We wanted to apply the same marking process and methodology to all containers. We had to go away and think about how that would work and make sure it was suitable for all the different processes that might be used. We tested many different approaches! For the discussion paper, we agreed that the preferred method should be a digital printing process and that the inks must be able to withstand process temperatures. Standard inks can be destroyed by sterilization temperatures, so inorganic inks are better. Laser systems can also be considered, but as mentioned previously, they can potentially impact on the container so this needs to be carefully considered.

In my view, there are three key things with serialization: readability, readability, and readability. If you cannot read the code then it is all pointless, so the code needs to be able to withstand all steps of the fill-finish process – as well as other tests, such as stability tests – and still be readable.

At Stevanato Group, our solution is a digital process that prints a GS1 ECC 200 2D data matrix barcode on the container after the forming process and immediately inspects it against a standard – rejecting it if necessary. That way, we know the code will be readable as it passes through the rest of the line and process steps internally and externally. You would not believe how many grey hairs I have from developing this process. It is not easy to get such a small barcode onto a glass container and ensure that it is readable in all circumstances.

As for the software requirements, we followed traditional serialization architecture. We have a Level 3 (L3) system that runs on the line, and a Level 4 (L4) system that works at a corporate level to create and manage the unique serial numbers throughout the life of the product

Also discussed in the paper is nest/container aggregation – which I think will be a novelty to the industry. I proposed the idea because it will make it easier to potentially implement this unique identifier approach on existing filling lines. Most syringe filling machines use a nest during the filling process. When reading the code on a syringe, you'll need to remove the syringe from the nest, ensure that it is facing the camera and that any systems do not affect the sterility and validation of the process. Product aggregation is a process that can overcome these issues by creating an electronic parent and child relationship between the container and the nest. The exact process for this is described in the paper for those who want the details…

What are the next steps?

There are huge benefits to introducing this concept and the ISPE has been very supportive.

To conclude, I would like to point you to the purpose of the ISPE document – to obtain your feedback on four areas:

1. Have all your potential use cases been covered? If not, what has been missed?
2. What are the perceived challenges of implementing this solution?
3. If there are challenges, how can they be overcome?
4. What additional discussion or data is needed for this to become the basis of a standard for the industry?

We eagerly anticipate your feedback!

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A Smaller Piece of PiE

How can manufacturers reduce the presence of pharmaceutical ingredients in the environment?

By Jonathan Rhone

The presence of pharmaceuticals in the environment (known as PiE) has become a global issue, with trace levels of APIs now widespread in rivers, lakes, groundwater, and, in some cases, drinking water worldwide. According to the WHO, we are now facing one of the most pressing health threats in modern times (1). As concerns grow, many in the pharma industry are beginning to re-evaluate their practices. But the challenge we must contend with is far from straightforward; rather it is a multifaceted puzzle that requires some background and context to accurately address.

APIs reach wastewater through multiple pathways – significant routes include human and animal excretion and the disposal of unused medicines by consumers. However, manufacturing effluent is another clearly identifiable point source pathway. Notably, such discharge can lead to localized hot spots downstream of manufacturing plants, which pose higher risks for aquatic organisms in the receiving water. A high-profile example is in the Hyderabad pharmaceutical cluster, where Swedish researchers found that large volumes of surface and groundwater were contaminated by antibiotic APIs (2). Ciprofloxacin was measured at up to 10,000 µg/L in rivers and 6,500 µg/L in lakes. Other studies have reported API hot spots downstream of manufacturing plants in the US, the EU, Taiwan, and Korea Given that the problem is recognized, what factors are hindering efforts to reduce the industry's overall environmental impact?

Regulatory disparities

One of the main drivers of the problem is a lack of regulation. There are more than 10,000 pharmaceutical manufacturing plants worldwide, with 80 percent of all APIs manufactured in India and China. However, standards and reporting requirements are poorly-defined, which creates an environment where practices vary significantly – not only on a national scale but internationally. In short, it is difficult to fully ascertain the extent of the problem.

That said, some regulatory guidelines do provide limited help. For example, environmental risk assessment standards for APIs are built into new drug approvals by the FDA and the EMA. Though the intent of such guidelines is to address the environmental impact from normal prescribed use rather than actual manufacturing processes, they have been applied to manufacturing effluent in many cases. For the US, this means that Environmental Assessments (EAs) must be submitted as part of most applications for new drugs, marketing approval for existing applications, and for various other actions defined by the FDA unless the action qualifies for exclusion. Environmental Risk Assessments (ERAs), as defined by the EMA, have tighter requirements. For example, the EMA's aquatic environment concentration threshold for exclusion is 0.01 µg/L. But even if the expected environmental concentration is lower than the threshold, manufacturers still need to complete the next phase of ERA if there is an expectation that the drug could affect the reproduction of vertebrates or lower animals.

"One of the main drivers of the problem is a lack of regulation."

Unfortunately, most drugs approved prior to October 2005 (when the guidelines first came into effect) have not been subject to these evaluations. There are several draft recommendations currently being considered by the EMA to not only bring these older generic drugs into the ERA framework but also to enhance the overall ERA requirements to further mitigate the potential impact on the environment and public health.

It is also important to note that, though the regulatory framework for GMP was developed to provide rigorous guidelines for pharmaceutical product quality and safety, it was never intended to include environmental criteria. And that means US and EU inspectors are unable to influence or control manufacturing discharge at pharmaceutical factories in developing countries with weak environmental standards and regulatory systems.

To be fair to the industry, even in the absence of manufacturing regulations for APIs, it is taking significant voluntary steps to make a difference. At the 2016 World Economic Forum, over 100

pharmaceutical and biotechnology companies and associations signed the Industry Declaration on Antimicrobial Resistance (AMR) as a collective commitment to combat the global threat of AMR to human health. The declaration was followed by the adoption of an Industry Roadmap for Progress on Combating AMR and the creation of the AMR Industry Alliance to research, develop, and implement solutions to address PiE. One of the outcomes of this work was the development of Predicted No-Effect Concentration (PNEC) values for APIs. PNECs are industry-recommended targets for API concentrations in water that are deemed safe for wildlife and receiving ecosystems. PNEC levels are very stringent, in many cases requiring treatment at 1 part per billion or higher. Another outcome of the initiative was the increased industry focus on reviewing and tightening API manufacturing supply chains and outsourcing standards to control the release of APIs into the environment. The Pharmaceutical Supply Chain Initiative (PSCI) also supports manufacturers by facilitating active collaboration with the AMR Industry Alliance, providing information about established PNEC values, and providing supply chain environmental audit guidance. Despite these systems being in place to help address the challenge, we need to examine the technology requirements more closely.

Current technology

APIs are chemically stable – often recalcitrant and nonbiodegradable. In many cases, this means that conventional on-site systems installed at pharmaceutical or municipal wastewater treatment plants (WWTP) are either ineffective or unable to treat them to the levels required to minimize environmental impact. These plants rely on primary (removal of solids via screens, grit chambers, and settling) and secondary (involves the use of biological processes like activated sludge and trickling filters) treatment processes whose efficiency varies from facility to facility. For example, though bacteria in secondary processes can break down some compounds or alter them enough to render them harmless, they don't completely remove all APIs. Some fail to be completely degraded by biological treatment while others will not degrade at all. Furthermore, some APIs are toxic and can kill the bacteria used, reducing the overall efficiency of the plant. Therefore, manufacturers must employ other

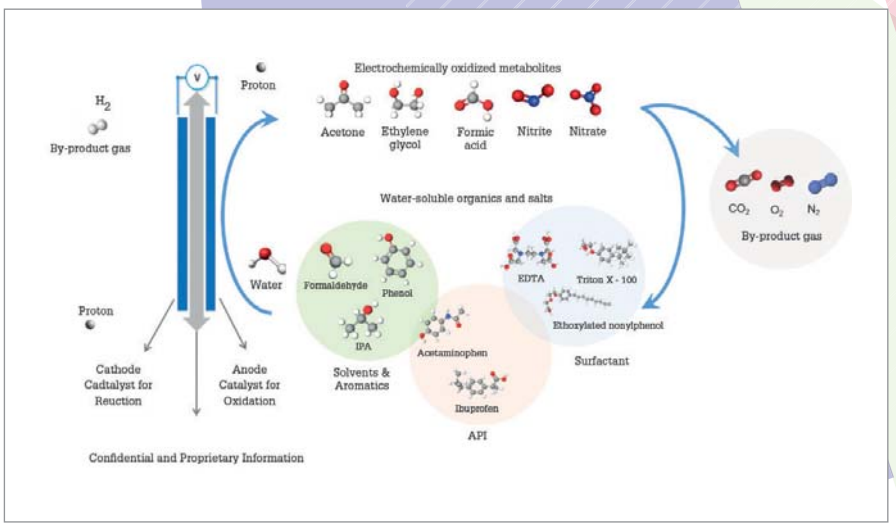

Figure 1. Graphical depiction of Axine anode and cathode processes during treatment

Figure 2. The redox processes at the anode and cathode of the electrolytic cell during treatment, and the transition of contaminants to intermediates and ultimately to by-product gases

disposal approaches as well as advanced treatment technologies to ensure that all APIs are destroyed before treated water is discharged into the environment.

The most common approaches for addressing API-contaminated wastewater are thermal oxidation, advanced oxidation processes (AOPs), evaporation, and activated carbon. Each of these approaches has advantages and disadvantages (see sidebar). But technologies capable of in-situ treatment, destruction, and verification of virtually any API to PNEC or non-detectable limits offer a newer approach to handling manufacturing effluent. We, for example, use proprietary electrochemical oxidation technology that lowers PiE levels without producing any residual liquid or solid waste. The core of our technology is the reactor (see Figure 1), which houses several electrochemical cells, each containing a pair of electrodes selected based on the specific wastewater application. When electricity is applied to the reactor, the positively charged anode electrode surfaces, directly and indirectly, oxidizes organic contaminants through multiple oxidation mechanisms (see Figure 2). Data analytics and automation software provide on-line, remote operation, performance monitoring, and verification. Contaminants are subsequently converted into intermediates, and ultimately to carbon dioxide, oxygen, hydrogen, and other trace by-product gases, which are vented.

"Though the right technology will help in tackling the industry's environmental footprint, work is required on multiple fronts to make a significant difference."

Evidently, there are many options for manufacturers to weigh up. However, companies need to keep in mind the fact that they will continue to receive intense scrutiny from all stakeholders including the public, government, NGOs, investors, and industry. Though the right technology will help in tackling the industry's environmental footprint, work is required on multiple fronts to make a significant difference. We all need to consider how we will continue to contribute to environmental research and commit ourselves to monitor wastewater and water quality; developing new drugs that pose

Traditional Approaches for Contaminant Removal

Thermal oxidation/incineration: Trucking and incineration of API-contaminated wastewater is a well-established practice in the pharmaceutical industry. Wastewater is collected in drums, totes, or tanks, transferred to trucks, and then transported, often hundreds of miles, to be incinerated at special waste facilities. Wastewater is conveyed to oil- or natural-gas-fired furnaces and incinerated at temperatures between 800 and 1,200˚C to ensure complete destruction of APIs. This approach is expensive, energy-intensive, and introduces risks associated with verifying the destruction of API contaminants. It is also frequently at odds with corporate sustainability goals aimed at reducing waste, lowering greenhouse gas emissions, and improving environmental performance.

Advanced oxidation processes (AOP): AOPs use chemicals to generate hydroxyl radicals (OH*), which oxidize APIs in wastewater into smaller organic molecules. Conventional AOPs include ozone combined with hydrogen peroxide (O_3/H_2O_2) and ultraviolet light combined with hydrogen peroxide (UV/H_2O_2). AOPs can be effective at treating some APIs at low concentration but are expensive to implement and have performance limitations. One of the main drawbacks of AOPs is they are often unable to achieve complete destruction of APIs to meet stringent PNEC values and can produce toxic oxidation by-products.

In the case of O_3/H_2O_2, ozone is typically generated on-site and is toxic, requiring rigorous monitoring and destruction. H_2O_2 is also a hazardous chemical with regulatory requirements for storage and handling. UV/H_2O_2 also requires significant upfront capital investment and has high operating costs including energy, UV lamp replacement, ballast replacement, and H_2O_2. In addition to the safety and regulatory considerations of H_2O_2, there is an additional requirement for disposing of UV lamps, which in most cases contain mercury.

Evaporation: Various types of evaporation systems use heat to reduce the overall volume of wastewater. The evaporated water can be collected as a clean distillate. However, evaporators do not treat or destroy the APIs; they concentrate the APIs in a liquid or solid waste stream that must be collected and transferred off-site for disposal and incineration. Evaporators are also capital intensive and generally suited to small-volume segmented streams. The presence of organics solvents can also be a limiting factor for the application of evaporators.

Activated carbon: Activated carbon is a media commonly used to adsorb natural and synthetic organic compounds from wastewater. In certain applications, it can be an effective treatment technology due to the highly porous nature and large surface area to which contaminants may adsorb onto the media. However, activated carbon is only effective on certain APIs and in most cases cannot reduce API levels in wastewater to PNEC levels. Like evaporation, activated carbon does not treat or destroy the APIs. The exhausted media must either be shipped off-site for disposal or regenerated on-site, which results in another API-contaminated waste stream that requires management and disposal. Activated carbon systems are also expensive to operate and maintain because the carbon media requires frequent replacement or regeneration.

less risk to the environment; creating an environmental certification standard for APIs in manufacturing effluent, and improving supply chain reporting.

Unlike other sources of pharmaceuticals in the environment, wastewater discharged from manufacturing plants is under the direct control of the industry. Proactive management of these emissions will not only reduce environmental and health risks but will also mitigate potential future risks, such as reputational damage, access to markets, as well as legal and financial liabilities. If we can take bold steps in the right direction today, we will have fewer repercussions to deal with in the years to come.

Jonathan Rhone is President and Chief Executive Officer of Axine Water Technologies

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Hello World!

Welcome to our Cell + Gene Curator roundup based on our ever-popular newsletter! Hot topics in the field this month include using CRISPR to engineer cell therapies and recent advances in bioengineering – key to unlocking the potential of regenerative medicine and tissue fabrication.

By James Strachan

Walter Isaacson writes about people who change the world. His biography of Franklin shows how he brought together the passionate Adams brothers, the rectitudinous Washington, and Jefferson and Hamilton's intellects to create the Constitution and Declaration. Similarly, his book on Steve Jobs shows his lasting impact on cell phones, personal computers, music, publishing, retail – the list goes on.

So it's telling that his next subject is none other than Jennifer Doudna – who, along with Emmanuelle Charpentier, won the Nobel Prize in Chemistry for her role in developing CRISPR. From what I've heard, The Code Breaker details Doudna's remarkable personal story, as well as discussing the future implications for gene editing.

"Suddenly after a billion years of evolution one species had the talent and also the temerity to edit its own genes – to hack its own evolution," said Isaacson.

Deciding, as a species, what we're going to do with CRISPR may be the defining issue of this century. But, let's not get wrapped up in sci-fi dystopias and focus instead on the significant positives: the end of debilitating diseases.

Engineering the future of oncology

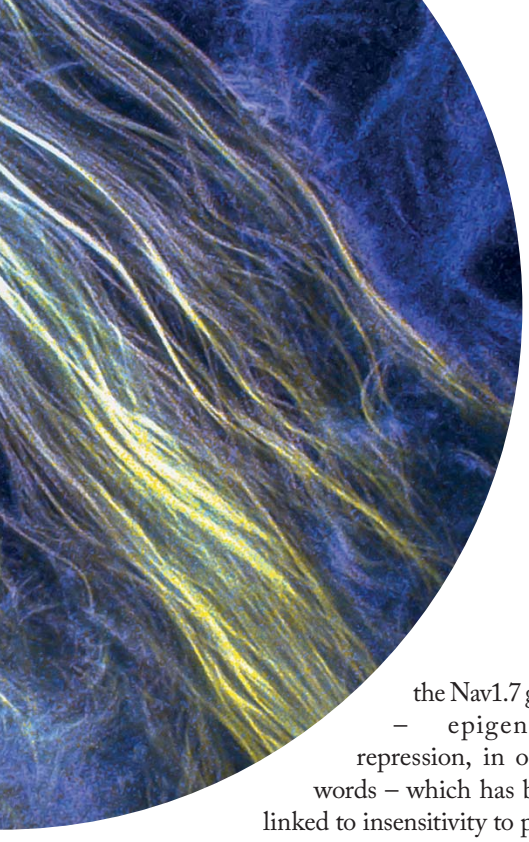
A current trend is using CRISPR to engineer cell therapies. For example, AbbVie has entered into a collaboration with Caribou Biosciences – which will use its CRISPR gene editing platform to engineer off-the-shelf CAR T cells with the ability to withstand host immune attack (1). AbbVie will then continue the programs into clinical development and commercialization. Let's see if the deal – worth $40 million upfront and up to $300 million in milestone payments – will bear fruit as quickly as AbbVie's 2018 deal with CALIBR, which has already led to clinical trials (2).

Another example in the research comes from Guangxi Medical University: a team there recently used CRISPR to design nanobody-based anti-CD105 CAR T cells for solid tumors. The CAR T cells prolonged the survival time of tumor-bearing mice and human tumor xenograft models (3).

We're also seeing a lot of improvements to the CRISPR system and new applications for the technology. Fred Hutch researchers developed "T cell optimized for packaging" (TOP) vectors for delivery of CRISPR-Cas9 to primary T cells that showed ~5–9-fold higher transduction efficiency than the commonly-used epHIV7 vector (4).

Meanwhile, Rice University researchers have developed a CRISPR/Cas9-based tool for editing the human epigenome – specifically histone phosphorylation. Their programmable chromatin kinase, called dCas9-dMSK1, allows for site-specific control over histone phosphorylation for the first time, and potentially opens the door to cracking the "histone code" – in other words, understanding how histones control gene expression. The researchers were also able to use dCas9-dMSK1 to identify seven new genes linked to melanoma resistance (5).

Continuing with the epigenome, a proof-of-concept study from the University of California San Diego suggests that CRISPR could be used to treat pain instead of opioids. The researchers used catalytically inactivated "dead" Cas9 (dCas9), which does not cut DNA, but maintains its ability to bind to the genome, and fused it to a repressor domain (KRAB). KRAB then temporarily repressed



the Nav1.7 gene – epigenetic repression, in other words – which has been linked to insensitivity to pain.

The result? Lowered pain sensitivity in mice lasting several months (6).

And in a brief departure from cell and gene therapy news, researchers from Columbia University in New York are using CRISPR to encode binary data into bacterial cells. By assigning different arrangements of DNA sequences to different letters of the alphabet, the team were able to encode the 12-byte text message "hello world!" into DNA inside E. coli cells. "This work establishes a direct digital-to-biological data storage framework, and advances our capacity for information exchange between silicon- and carbon-based entities," said the study authors (7).

Mighty morphin' biomaterials

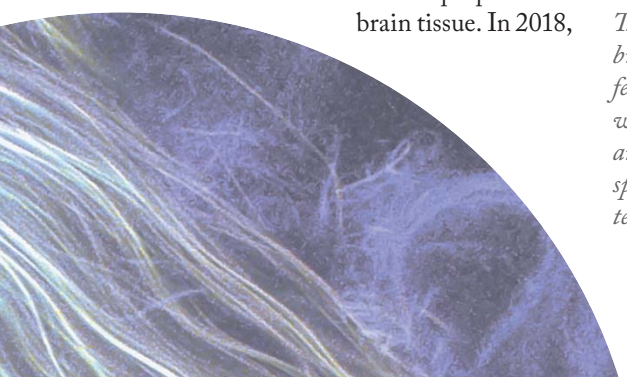
Elsewhere, a number of advances have been made in biomaterials and 3D printing for regenerative medicine. A Northwestern University team has discovered a new printable biomaterial that mimics the properties of brain tissue. In 2018, the group reported the phenomenon of molecular reshuffling, where molecules migrate over long distances and self-organize to form larger, "superstructured" bundles of nanofibers. Now, they've shown that these superstructures can enhance neuron growth (8). The ultimate aim is to grow healthy neurons from a patient's own cells using these superstructure-enhanced biomaterials, and transplant them into the brains of patients with neurodegenerative conditions.

In a related story, researchers at the University of Illinois at Chicago describe their new bioengineering material as "4D", which means it changes shape over time in response to stimuli – it can morph multiple times in a preprogrammed fashion or in response to external trigger signals. And that could allow the researchers to engineer tissue architectures that more closely resemble native tissues (9).

Researchers at Lund University in Sweden also designed a new bioink, which allows for 3D printing of small human-sized airways that support growth of blood vessels into the transplanted material (10).

Finally, Carnegie Mellon University researchers have developed a new 3D-bioprinting method that could enable the fabrication of adult-sized tissues and organs (11). The Freeform Reversible Embedding of Suspended Hydrogels (FRESH) approach involves a yield-stress support bath that holds bioinks in place until they are cured. This prevents distortion of bioinks, which results in a loss of fidelity – a major barrier to advanced tissue fabrication.

This article is based on a selection of the breakthroughs that have recently been featured in The Cell + Gene Curator – a weekly newsletter covering the latest news and research in the cell and gene therapy space. Subscribe for free at: https://www.texerenewsletters.com/cellandgene



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The Only Science Is Good Science

Sitting Down With… Johannes Khinast, CEO and Scientific Director of the Research Center for Pharmaceutical Engineering (RCPE), Graz, Austria

What influenced you to launch RCPE in 2008?

The idea was simple: I wanted to conduct research that could be applied to pharmaceutical manufacturing. I gained feedback on interest in such a center at the University of Graz and we had a tremendous response from pharmaceutical companies. They told us this type of center was "exactly" what they needed! We started with just three people and now we have over 160 – and we're still growing. At the beginning, it was like baking cookies with friends, but we've professionalized the center over the years. We have created groups within the center and we have leaders of those groups – and our work is internationally visible; we push out a lot of publications. But we don't take money and bend the work towards that. We would rather do good science – and then the money flows to us! We have four main areas of focus: modeling and prediction; advanced products and delivery; process and manufacturing science; and continuous flow synthesis and processing.

You recently received funding from the FDA…

That's right. And I'll note that it's super unusual for an EU company to receive FDA funding (only around one percent of these grants are given to non-US companies). We were fortunate in that we were working with many US companies, such Pfizer and MSD, who suggested we put a proposal together. We did a great job and got funding for two projects: digital simulation tools for drug product manufacturing and process development; and optical coherence tomography for real-time monitoring and control of the tablet coating process.

I've been pushing the concept of digital twins for a long time – so I consider the first project to be a personal success; it's fantastic for the center's expertise in this field to be recognized. The industry needs to move away from empirical trial and error approaches. There are big benefits in powerful simulation coding combined with good understanding of material properties.

The second project is about using sensors to understand coating quality, measure coating quality, and control it in real time. It's a completely new sensing concept, which was not invented by us, but taken from another field and applied as a real-time tool. Coating is a very old process, but a lot of things can go wrong, so it's an area that deserves more attention.

How did you get into the pharma industry initially?

In all honesty, it was partly because I was a little lazy! When I was a young professor at Rutgers University in New Jersey, many of my colleagues were working with big oil and gas companies – and they had to travel a lot. I preferred to stay local, and New Jersey is a hotspot of pharmaceutical development. It was quite new at the time for a chemical engineer to work with pharma companies, but it created a new field.

What else are you working on right now?

Many things! I'm very excited about nano-based manufacturing. We're also working on spray drying of proteins and a big demonstration plan for continuous manufacturing – for both the API and downstream manufacturing. We also have a focus on individualized manufacturing – such as how to make small batches or even a single pill for a patient. We've designed a system that can make a single pill for a single person in around 40 seconds. I realize that's actually very slow – but there are huge amounts of potential for accelerating the process.

What are your thoughts on the future of drug manufacturing?

There's no doubt in my mind that we need to have continuous processes in almost all aspects, with quality assured in real time. The old paradigm of batch manufacturing leads to super-long supply chains, which are risky and costly. We need to reduce the size of technology and create processes that continuously make drugs.

My personal prediction is that, maybe 20 or 30 years from now, we will have small molecules with the same selectivity and activity as large biomolecules. Biologics are very selective and can do amazing things, but they are also very expensive and sensitive, which makes them difficult to manufacture and transport. I think there is room for new modalities based on small molecules. Eventually, perhaps we can replace biomolecules with these new generations of small molecules… The pipeline for small molecules is still very good and there is a lot of innovation.

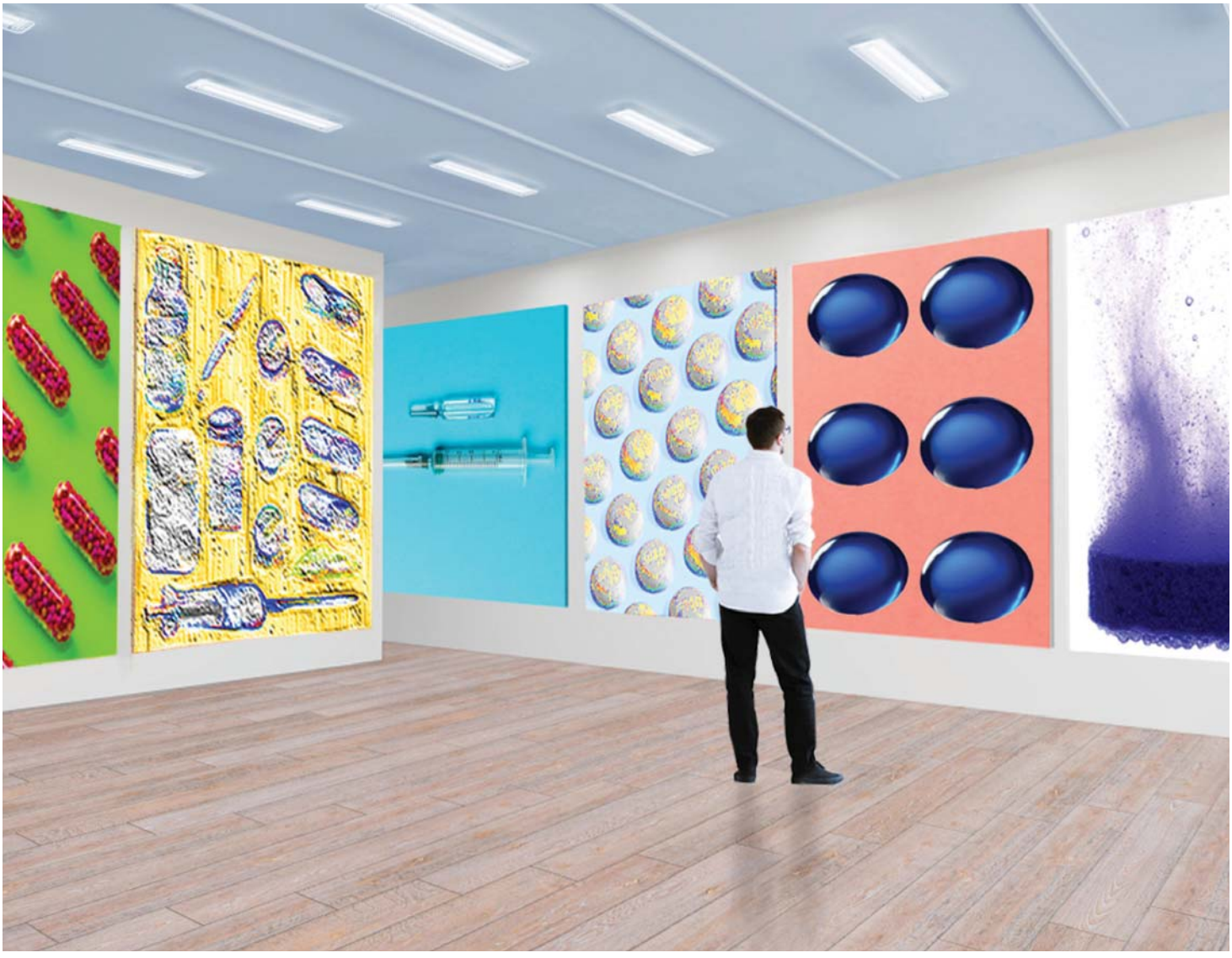
Almost certainly, we will be making drugs in completely different ways in the future – faster, with fewer people, and a lower environmental impact.

How receptive do you find pharma companies to new technologies and approaches?

In my experience, innovation is very much appreciated. There is a stereotype that pharmaceutical companies are very conservative – and they are because they should be! But if you create something that is really helpful, companies are typically open to innovation. I've had great experiences working with pharma companies to bring new technology into their manufacturing plants.

How do you feel when you look back and think about how RCPE has grown over the years?

I really didn't expect it. And it still feels like I'm in a movie sometimes! Nevertheless, I do believe that RCPE is the premier research center in the world! There are other similar centers around the world that are university based, but their great PhD and postdoc students take all their knowledge when they inevitably leave. We have permanent jobs here rather than just relying on students. And we have good people from all over the world in many disciplines – good physicists, good programmers, good pharmaceutical scientists and engineers, and good biologists – and that allows us to take a multidisciplinary approach to projects. I am extremely proud of how far we have come.



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