NOVEMBER / DECEMBER 2022 # 88

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The Innovation Awards 2022

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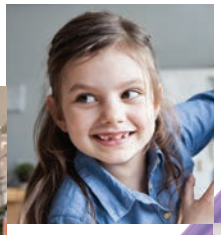

Words from the Wise

Five quotes to end the year in style – and thoughtfulness

The best part of my job is talking to so many fascinating and passionate people – listening to company and career origin stories, exploring research and new technologies, and finding inspiration both in progress so far and bold hopes for the future. For my final editorial of 2022, I look back on some of those key conversations to find five thought-provoking quotes that are worth sharing.

"If a company wishes to determine its future, it must understand its past. Success necessitates an understanding of who you are, how you became who you are, and continuous investment in your future." – Thomas Otto, Vetter Pharma-Fertigung (1)

"When you look at therapies today, there are new dosage forms and breakthrough therapies that simply didn't exist 20 years ago, such as targeted immunotherapy agents and certain combination products. They require unique formulation solutions – and that means more novel excipients." – Meera Raghuram, Lubrizol (2)

"In the last few years, there has been an exciting change; more companies are trying to implement sustainability over the entire lifecycle of making a drug, with the notion that health is connected to environmental sustainability. If we're really serious about healthy patients, we have to have a healthy planet." – Kristi Budzinski, Chemical Society Green Chemistry Institute Pharmaceutical Roundtable (3)

"One new trend is a desire among clients to future-proof their facilities. Given the recent wave of disasters, they want to expect the unexpected." - Ian Lichfield, WHP (4)

"Watson, Crick, and Franklin identified the structure of DNA in 1953. Twenty one years later, I started medical school. Across six years of studying biochemistry, I received one lecture on DNA. I remember it very clearly. It was mainly limited to the topic of structure, but at the end of the lecture the professor said, "Look, one day, this DNA structure might be useful." Twenty years later, I formed a company based on DNA gene therapy, and fell one hair short of bringing it to market. Now, in 2022, with some help from my consultancy, 10 approved gene therapies exist. So my professor was right – that DNA stuff did prove useful. It just needed time – albeit forty years' worth!" – Alan Boyd, Boyds (5)

If you want to share your own wisdom on any topic connected to (bio)pharmaceutical drug development and manufacturing, don't hesitate to drop me a line: stephanie.sutton@texerepublishing.com

Stephanie Sutton
Editor

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2. *The Medicine Maker, "Moving Away From "Quality by Fear": Part I," (2022). Available at https://bit.ly/3Bdkk9A.*
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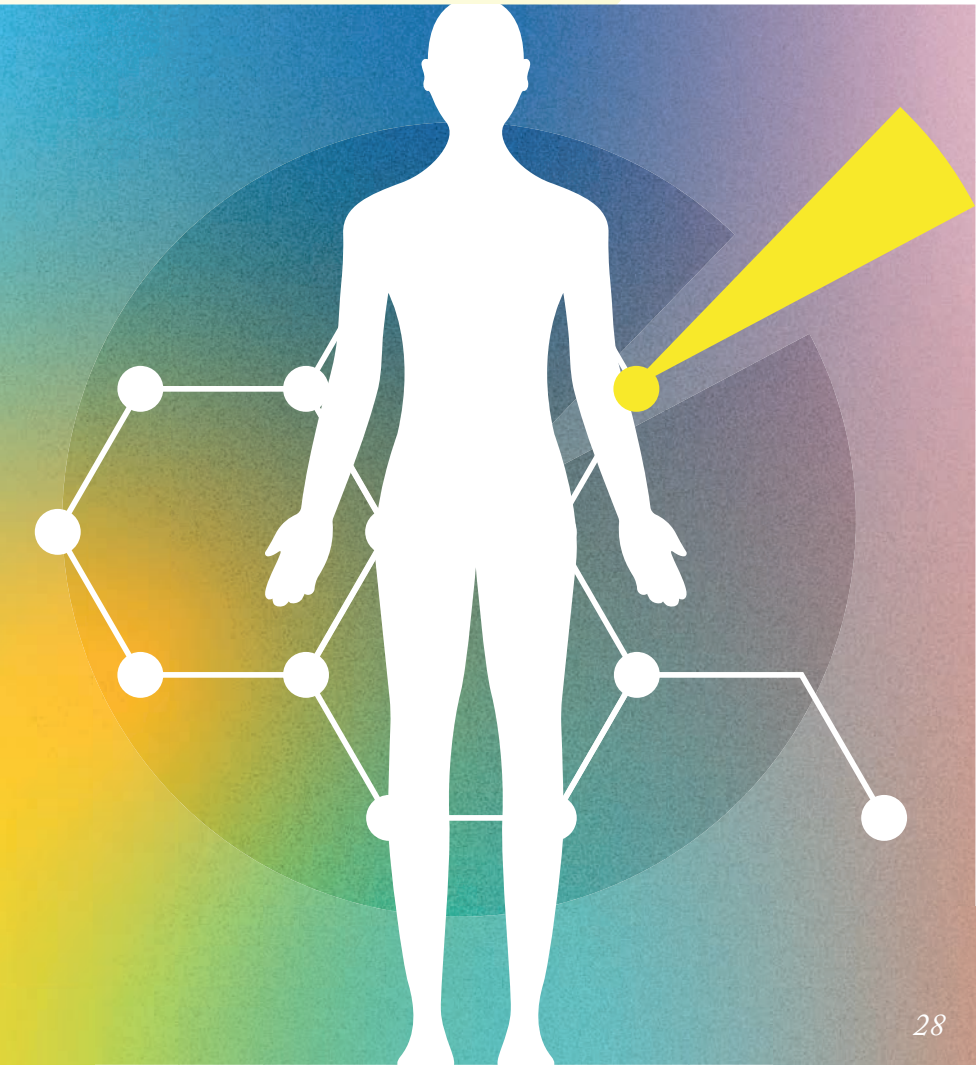

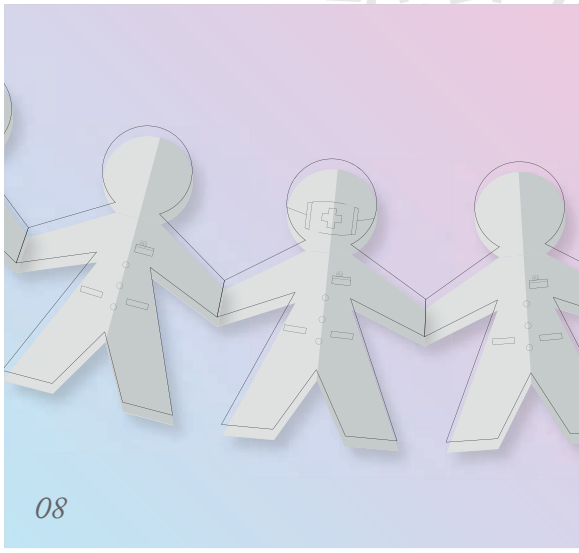

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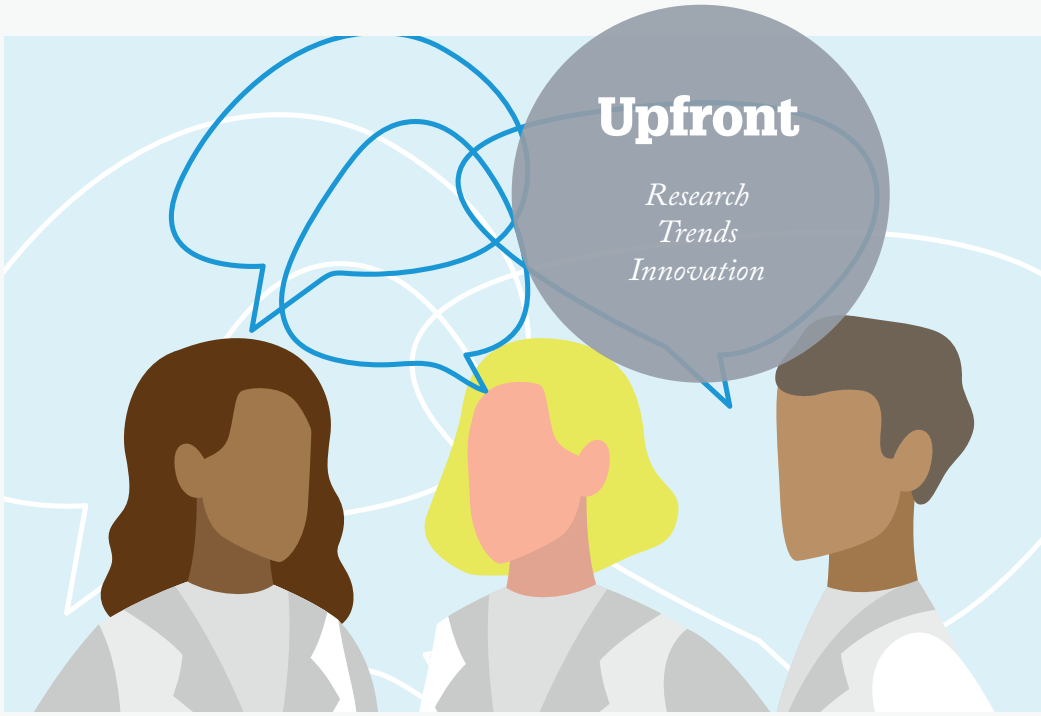


Social Medicine

Gathering medical data from social media could change the game for tailored medicines, but there will be opposition

The Pistoia Alliance has launched a Community of Experts to harness data from social media with the aim of advancing patient-centric drug development. The initiative was proposed by member company Semalytix and supported by representatives of other big pharma members.

Technology and data experts are now being invited to help develop a framework, but those familiar with social media will know what a toxic and divided space it can be. Whilst social media can be used for friendly and decent purposes, such as sharing legitimate medical experiences, there is a resident evil that manifests itself in contrarianism and misinformation. The data experts will be tasked with separating the fakes from the facts to listen to the genuine concerns and experiences of patients.

Both the FDA and the EMA have acknowledged online patient experience research as a powerful tool for collecting data for patient-focused drug development. Yet, this in itself is a carrot-on-a-stick for the bots and trolls, who do not always take kindly to global organizations harvesting data. The increasing use of social media by both private and public sector stakeholders has led to conspiracy theories and generated what the WHO labelled as an "infodemic" in 2020.

In a statement, Semalytix CTO Philipp Cimiano said: "State-of-the-art natural language processing has advanced to enable us to conduct retrospective online patient experience studies using social media as a way to inform product development activities. Current methods allow us to carry out such studies in a scalable fashion, capturing the voices of thousands of patients, to identify patients' unmet needs, concerns, and priorities, as well as what would be meaningful improvements."

Another challenge lies in the fact that patients do not communicate in the same way as medical professionals, and can use very simplistic terms on social media, so it will be interesting to see how the framework will access and leverage the information mined.

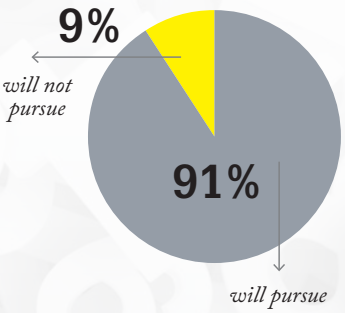
The project lead at the Pistoia Alliance, Thierry Escudier, acknowledges the complexity of the challenge: "We are keen to get as much expertise as possible on this complex initiative, particularly RWD experts and technology companies. This data has the potential to be hugely insightful and impactful across the drug development pipeline."

INFOGRAPHIC

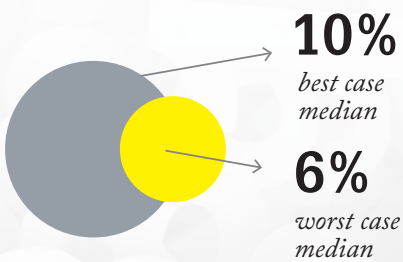
2022: The Numbers Speak

Stats from an industry survey lend insight into the state of pharma in 2022 – from modalities to facilities

Percentage of companies pursuing multiple therapy modality in one building



Respondents' growth rate predictions



BUSINESS - IN BRIEF

Biosimilars in the US, the EU's DARWIN project, and a Twitter debacle… Here's what's going on in the business side of the pharma industry

- In the US, Senator Mike Lee is looking to make all approved biosimilars interchangeable, without the need for switching studies, with a new potential bill called the Biosimilar Red Tape Elimination Act. In a statement, Lee said, "Our regulatory environment is making it too difficult and expensive for biosimilars to make it to the market. Ultimately, it's the patients who suffer from a lack of competition and high drug prices."
- Data partners have been selected for the EMA's new DARWIN EU project – the Data Analysis and Real-World Interrogation Network. Data will be made available to the partners to generate real world evidence to support scientific evaluation and regulatory decision-making.
- The FDA has published a new report titled, Successes and Opportunities in Modeling & Simulation for FDA. The report presents various modelling and simulation case studies from the agency, including how in silico modelling-based approaches can predict toxicity endpoints, predicting the safety of drug impurities, premarket product quality assessments, and much more.

- Insulin prices are back in the spotlight after a Twitter account posing as Eli Lilly tweeted, "We are excited to announce insulin is free now." The company's stock price dropped. A writer called Sean Morrow has claimed responsibility for the tweet, claiming that he wanted to drive home the "absurdity" of insulin prices.
- Teva Pharmaceuticals has appointed Richard Francis as its new President and CEO, effective January 1, 2023. Francis will replace Kåre Schultz and has previously served as CEO of Sandoz and a member of the Novartis executive team.

ADC Adversity

Meta-analysis of ADCs explores potential for adverse effects

ADCs have made significant progress in oncology in recent years. Their rapidly increasing use in the clinic, as well as in numerous ongoing trials exploring their further use, has inspired researchers to meta-analyze their potential adverse effects.

Researchers at Xiangya Hospital, Changsha, China have studied the occurrence of serious side effects relating to the receipt of ADCs. Data from 169 clinical trials involving 22,492 patients were reviewed to determine the treatment-related causes of higher toxicity and adverse events in patients. The study indicates that different ADCs have various adverse events. The comprehensive data obtained by the research could provide an important reference for both clinicians and patients on how to care for toxicities from ADCs in clinical practice.

Reference

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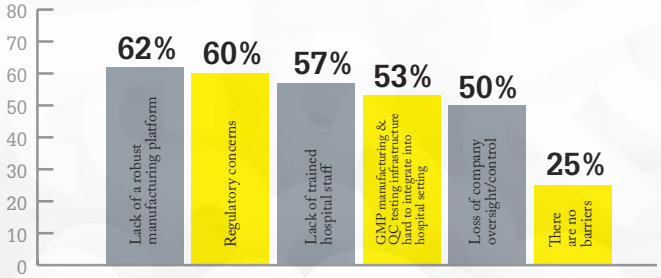
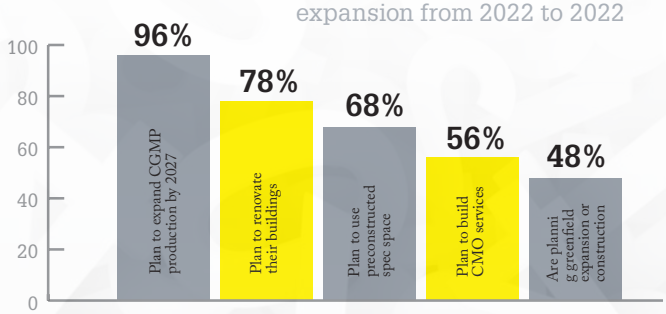
Perceived barriers in point-of-care cell therapy manufacturing



Respondents' plans for expansion from 2022 to 2022



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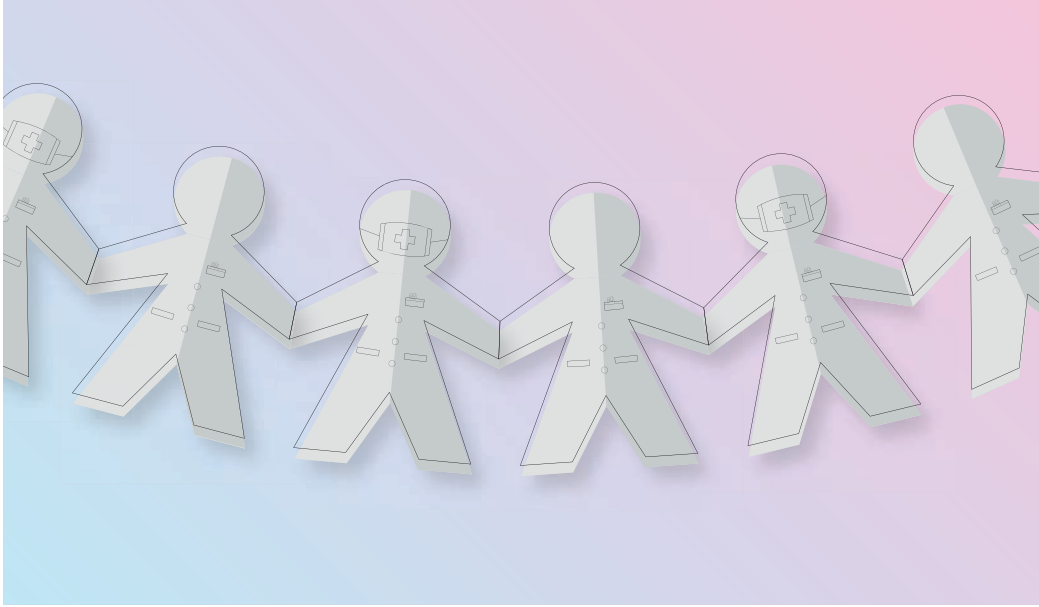

The Human Cost of Poor Practice

The growing number of deaths linked to pediatric medicines prompts the WHO to investigate "unacceptable" levels of APIs

On October 5, 2022, The WHO alerted authorities in The Gambia to a batch of pediatric medicines contaminated with "unacceptable amounts of diethylene glycol and ethylene glycol," which resulted in the deaths of 66 children (1). The medicines in question? A selection of simple cough remedies.

Monitoring and preserving the health and safety of children is the cardinal responsibility of parenthood, but not everybody can be a doctor, a scientist, or a manufacturer of medicines. Parents therefore place trust in those who can. And when a cough syrup arrives on the shelves of a local pharmacy or supermarket, trust is placed in those who have regulated and approved its use and those who control the supply chain. Most poignant of all, when that syrup is poured onto a spoon, a child places their trust in the parent.

India-based pharmaceutical manufacturer Maiden Pharmaceuticals Limited provided the medicines, but were apparently reluctant to provide safety and quality guarantees. Following laboratory analysis, WHO experts confirmed the presence of dangerous amounts of diethylene glycol and ethylene glycol – both of which can be found in automotive products, such as antifreeze and brake fluids, solvents and paints.

On October 20, a similar outbreak of acute kidney injuries was reported in Indonesia, where (as of November 4) 190 children were confirmed dead following symptoms, prompting the government there to suspend sales of all syrup and liquid medication (2). The same APIs were present. Officials in Jakarta are now considering criminal action against the pharmaceutical companies responsible for manufacturing the products, although these brands and respective companies have not been named as they were in the Gambia case. What we do know is that Indonesia imports most of its raw ingredients from India and China, suggesting a potential link.

Any legal repercussions for the business may be catastrophic, but paltry compared with the lost trust in pharmaceutical supply chains, and insignificant when considered alongside the death of innocents.

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2. *Reuters, "Indonesia may seek prosecution of pharma firms as child AKI deaths rise" (2022). Available at: https://reut.rs/3suePhO*

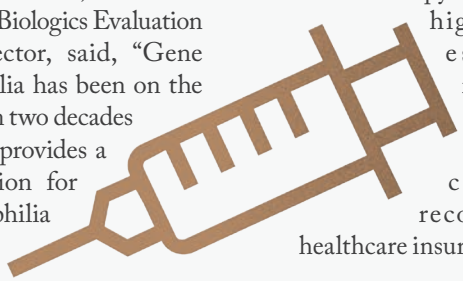
Bleed American

Hemgenix – the $3.5 million Hemophilia B treatment

Preferring not to mention prices in its press release and focussing instead on the threat of hemophilia, as well as all the gory symptomatic details and the benefits of treatment, the FDA has granted Priority Review, Orphan, and Breakthrough Therapy designations in its approval of a new adeno-associated virus vector-based gene therapy, Hemgenix, which is manufactured by CSL Behring and uniQure.

In a statement, Peter Marks, Director of the FDA's Center for Biologics Evaluation and Research Director, said, "Gene therapy for hemophilia has been on the horizon for more than two decades … Today's approval provides a new treatment option for patients with Hemophilia B and represents important progress in the development of innovative therapies for those experiencing a high burden of disease associated with this form of hemophilia."

But the therapy will come with a high price tag: an estimated $3.5 million per dose. Hemophiliacs across the US could well be reconsidering their healthcare insurance contributions.



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Team TMM members Lauren Williams and Brice Agamemnon living it up at CPHI 2022.
Credit: Brice Agamemmon

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QUOTE of the month

"The record number of children under-immunized and susceptible to measles shows the profound damage immunization systems have sustained during the COVID-19 pandemic."

Rochelle P. Walensky, CDC Director, commenting on the measles threat in a joint statement from WHO and CDC

Enter #DiedSuddenly, Stage Right

Anti-vax documentary created by reactionary conspiracy theorists causes online stir

On November 21, a new video appeared on "alt" video sharing site, Rumble. That video was Died Suddenly, a 78 minute documentary created by right wing conspiracy theorist, Stew Peters. The film's central claim is that global elites are using COVID-19 vaccines as a tool to further their alleged goal of controlling world population growth. Peters' production argues that deaths caused by the vaccines are no accident, and far more common than the public realizes. However, in less than 24 hours, viewers with functioning critical faculties had already picked apart the film's heavy reliance on logical fallacies, uncited evidence, and a casual relationship with the truth.

Incidentally (or not), Rumble also runs a cloud hosting service best known for hosting Truth Social, the social media platform founded by Donald Trump.

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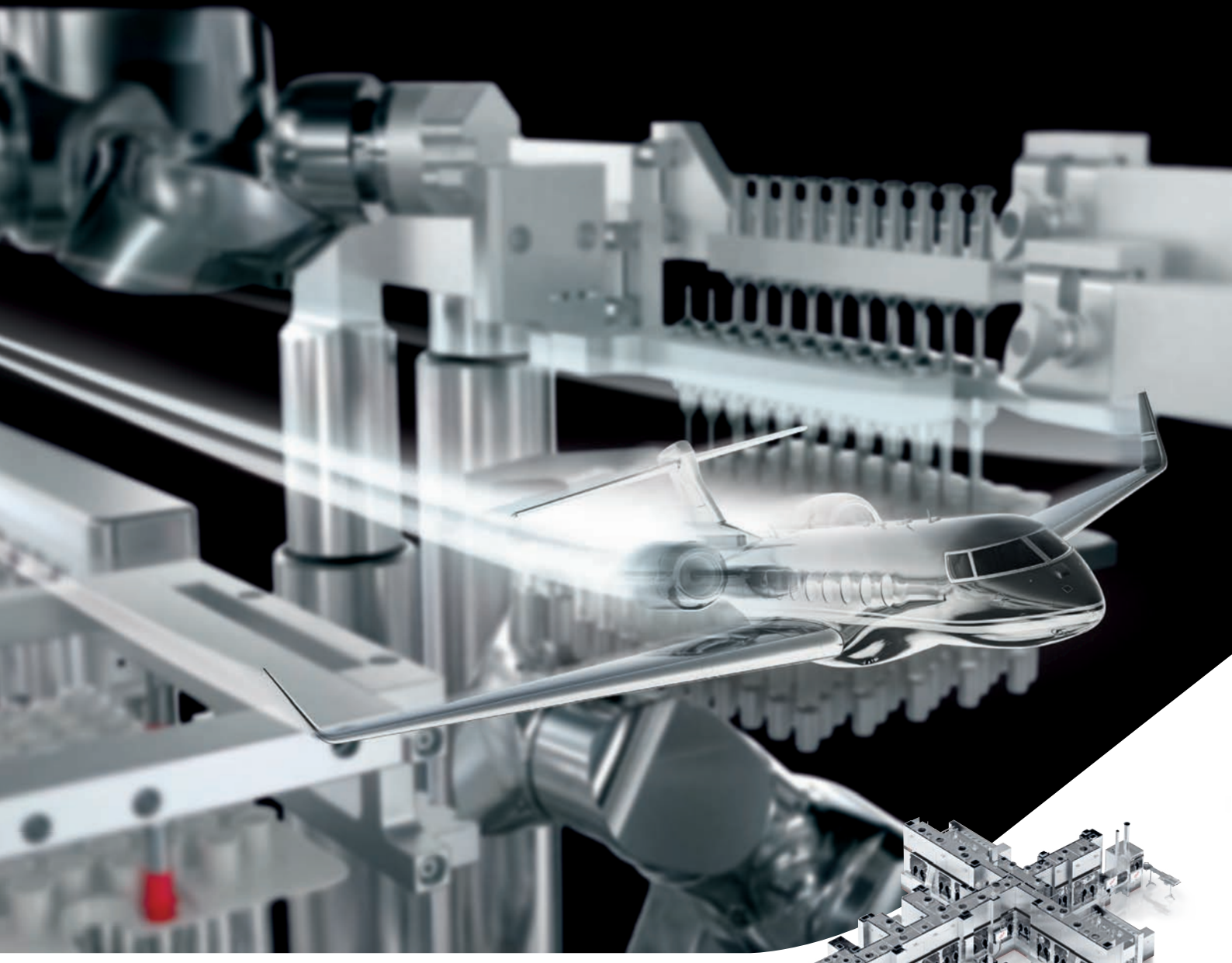

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In My View

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

Getting Started With Digitization

It's time for quality and manufacturing to go paperless, but how should a company go about digitization?

By Erin Wright, Vice President of Product, MasterControl, Salt Lake City, Utah, USA

Anders Sorman-Nilsson – futurist, author of Digilogue, and keynote speaker at MasterControl's 2022 Masters Conference – writes that "Change doesn't care whether you like it or not. It happens without your permission (1)." The impact of COVID-19 shows there is no question that digital transformation is a timely development and will be an ongoing necessity for pharmaceutical manufacturers to remain competitive.

Digitization is both an imperative and a buzzword. Depending on where you fall on the digital spectrum, it may bring relief, frustration, or uncertainty. It is commonly known (and supported by research) that companies hoping to ride out current upheavals and establish a sustainable presence must be able and willing to undergo digital transformation. A 2020 Harvard Business Review study, Rethinking Digital Transformation, states, "The drive for digital transformation has only intensified and become more essential for business success. Ninety-five percent of [700] executives surveyed say it has grown in importance… with 70 percent describing the change as significant (2)." It further states that transformation leaders report "revenues have grown significantly as a result of digital transformation, and they surpassed their peers by double-digit rates in other key areas, including operational efficiency, competitiveness, and customer retention rates."

Change is never easy, but it doesn't have to be overwhelming. Rest assured that there are proven and actionable steps to follow to efficiently complete a digitization project. Not knowing where to start can sometimes be the biggest hurdle.

One practical way to tip the scale in your favor is to start with solutions that are configurable off-the-shelf (COTS) and don't require custom code. Technology has come a long way in the last 10 years, so don't be afraid to discover and compare possibilities you weren't aware of. Many of today's quality and manufacturing software solutions are both configurable and purpose-built, which allows you to map to your existing processes instead of changing a process to match the software. A good configurable solution should allow you to automate and leverage master templates and complete digital forms designed to reduce human input errors.

My other piece of advice is to look for a cloud-based Software as a Service (SaaS). Corporate "no-cloud" policies are as rare today as "no-Internet" policies (3), but this comes with advantages such as enabling access from anywhere and reducing the initial outlay (but being able to add new capabilities as required). Upfront IT infrastructure and support are also minimal and employees can collaborate within the system. Accenture reports that 65 percent of leading cloud technology adopters saw 10 percent in cost savings from cloud migration and outpaced their peers in cost reduction by 1.2 to 2.7 times (4).

In the true spirit of transformation, it will not serve you to adopt digitization until you have evaluated and refined your current quality and manufacturing processes. Digitizing bad processes just makes for a bad digital solution, no matter how advanced the solution is. You must be willing to let go of outdated and inefficient processes. Likewise, get to the heart of the processes and focus on what is integral and valuable. Don't change what is good for the sake of being new and different. However, you should evaluate the efficiency of any process you plan to maintain. Are there missing links or redundancies? Can you streamline and connect currently fragmented processes? Make all the changes you can prior to implementing your solution to make it even more impactful. This type of pre-adoption strategy makes transformation easier to sustain after implementation. The solution you choose and configure should reflect your best workflow practices and allow you to modify them over time as needed.

When it comes to prioritizing digitization tasks, begin with your key quality indicators. Is it training? Is it electronic batch records? Try to align these priorities with current capabilities (i.e. budget, staffing, etc.) to create a list of steps you can complete one at a time. As you check off projects and your teams experience success, each subsequent project becomes easier and brings your company closer to complete digitization.

Remember – it takes a village, but you need a leader or else digitization projects will be deprioritized. Appoint someone to this role with direct support from upper management to ensure your efforts stay on track. Your leader should collaborate with affected departments and seek cross-functional input and engagement. An inclusive approach to innovation will create a sense of ownership in each department and improve adoption rates.

References available online online at tmm.txp.to/digitiz

Getting to Grips with mRNA

Walking through the mRNA manufacturing process – and its many challenges

By Catherine Jomary, Technology Lead ATMPs, IPS-Integrated Project Services GmbH, Basel, Switzerland

The groundwork of over three decades of mRNA research laid the foundations for the successful manufacture of the mRNA-based vaccines for SARS-CoV-2 – the first commercial realization of the technology. Going forward, mRNA technology will not only help the development of other vaccines for infectious diseases, but also address non-viral cell and gene therapy applications for diseases with unmet needs. The strong safety benefit of mRNA resides in the fact that it does not integrate into the human genome.

The process of producing mRNA from a DNA template is cell-free and scalable, but plasmid DNA (pDNA) manufacturing requires microbial fermentation. Even synthetic DNA synthesis requires pDNA as the starting material. The full manufacturing process from DNA template to mRNA encompasses three main stages.

First, the target DNA sequence (corresponding to the protein of interest) is introduced into a plasmid. This plasmid is then amplified using bacterial fermentation, purified, and linearized.

Second, the mRNA is synthesized during an enzymatic reaction called in vitro transcription (IVT). The template – linearized pDNA (which contains the target DNA sequence) – nucleotides, and enzymes are mixed together. The resulting transcribed mRNAs are then purified from the reaction contaminants using chromatography, tangential filtration, and sterile filtration.

Third, the mRNA molecules are encapsulated. The combined final product is purified and concentrated using chromatography and tangential flow filtration prior to sterilization and filling.

It sounds simple enough – and companies such as Moderna and Pfizer/BioNTech have shown us that manufacturing can be performed quickly – but there are many challenges along the way.

mRNA is relatively unstable and rapidly cleared after injection in vivo. To minimize such rapid degradation, modified nucleotides are utilized during IVT. However, most of these raw materials fall under a license fee, which increases the cost of manufacturing. To stabilize and allow efficient mRNA transduction post-injection in vivo, each end of the newly synthesized mRNAs needs to also be modified using specific methods that require the purchase of licenses – again, adding cost to the manufacturing process.

Being highly sensitive to rapid degradation during manufacturing, mRNA also needs to be stabilized and formulated to induce rapid uptake and host protein expression post injection. Blending of mRNA with delivery systems, such as a combination of lipids and polymers has been shown to protect mRNA from degradation, enhance cell uptake, and improve mRNA therapeutic potency. Lipid nanoparticles (LNP) are the most commonly used mRNA cell delivery system; each LNP consists of at least four different lipids that not only carry the mRNA but also form a protective barrier against degradation by the immune system. Producing LNPs with consistent particle size is a challenge that requires a tightly controlled technology. Currently, only a few companies provide such essential raw materials – and only at a limited scale. LNPs may require cold chain logistics for storage and delivery, which need to be taken into consideration when designing the manufacturing facility and supply chain distribution.

The full mRNA manufacturing process can be performed by a network of outsourcing partners. Alternatively, developers can choose to outsource some of the more specialized steps, such as pDNA and LNPs. Design of manufacturing facilities will be driven by the developer's strategy, but the full process workflow should be separated into at least three manufacturing clean room entities for pDNA, mRNA synthesis, and LNP encapsulation.

mRNA has come a long way since the start of the COVID-19 pandemic, with many lessons learned. But there is still more to do. In my view, current IVT mRNA manufacturing technologies have technical limitations and we must move towards more industrialized cost-effective processes. We also need to find a way to overcome supply issues in the industry. Flexible manufacturing platforms for mRNA can be established using single-use equipment formats and fittings – and many are currently available off-the-shelf from suppliers. However, SARS-CoV-2 mRNA vaccine production has created enormous pressure on the single-use and raw materials demand and resulted in long delivery lead times.

What can be done in the meantime? Developers of mRNA technology must have the end goal in mind when embarking on a new mRNA manufacturing project. A well-defined product profile will help you understand the challenges associated with the likelihood of manufacturing process changes throughout clinical phases up to commercialization – and put you in a better place for future success.

the Medicine Maker

INNOVATION AWARDS

INNOVATION ABOUND!

It's December – and that means it's time for The Medicine Maker to welcome you to 2022's most innovative new technologies in drug development and manufacturing – as nominated by the community.

But the celebrations are far from over – you also get to decide which of these innovations is truly the cream of the crop. Simply read through the summaries below and complete the form online at tmm.txp.to/innov-awards-2022.

Voting will close on March 16, 2023 – and the winning company will share the story behind the innovation in a 2023 edition of The Medicine Maker.

Without further ado, let's take a look at the 2022 shortlist…

APISOLEX POLYMER

Injectable-grade, polyamino acid-based, solubility-enhancing excipient

Produced by Lubrizol Life Science Health

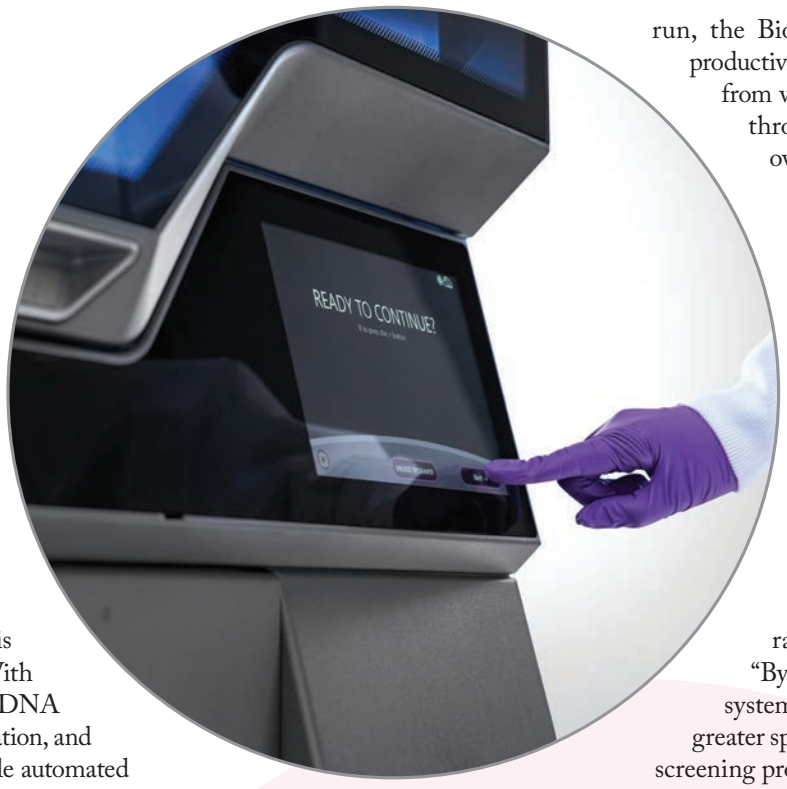
One of only a few solubility-enhancing excipients introduced for use in parenteral applications in the last 20 years, Apisolex Polymer uses straightforward, scalable formulation techniques. The excipient is a generally applicable micellar technology used to enhance the solubility of APIs – it is capable of increasing the solubility of hydrophobic APIs by more than 50,000-fold. It is designed to work with simple formulation techniques, with a view to streamlining manufacturing and minimizing API loss with a high encapsulation rate. With just a few ingredients, formulators can rapidly dissolve, mix, sterile filter, and lyophilize to obtain an injectable API. When lyophilized, drug products using the excipient will reconstitute in saline in under 30 seconds. Apisolex Polymer also provides higher drug loading – up to 40:100 API:solubilizer ratio compared with 1:100 for alternatives.

In 2019, parenteral formulations comprised 42 percent of new molecular entities (NMEs) approved by the FDA. As pharma looks to meet patient-centric demands and increased personalization, the number of parenteral formulations will likely increase, so excipients that can help expedite reformulation and repurposing of APIs via the 505(b)(2) pathway could have a significant impact on drug development.

BIOXP 9600

Synthetic biology workstation for accelerating synthesis of genes, clones, and variant libraries

Produced by Telesis Bio



The BioXp 9600 builds on the company's BioXp system platform and further accelerates iterative design-build-test product development cycles by enabling automated, rapid, high-throughput biology synthesis from digital sequences. With hands-free, high-fidelity DNA assembly, cloning, amplification, and mRNA synthesis in a single automated run, the BioXp system can improve productivity, reduce turnaround time from weeks to days, and increase throughput up to 96 samples overnight.

In an RNAimmune Inc. case study identifying mRNA vaccine candidates for infectious diseases, Associate Director David Brown shared how the BioXp platform further optimized the discovery process. One of the bottlenecks identified involved building or obtaining synthetic constructs for rapid candidate screening: "By using the BioXp automated system, we were able to achieve greater speed and throughput in our screening process," said Brown.

BYLOK TECHNOLOGY

Solving the light-heavy chain mispairing challenge in bispecific antibody manufacturing

Produced by Lonza

Manufacturing bispecific antibodies (bsAbs) poses unique and largely unsolved challenges related to their expression and downstream processing. As bsAbs comprise two distinct heavy and light chains, multiple combinations are possible during assembly. Mispairing between light and heavy chains during expression could lead to misassembled and unwanted antibody species that are difficult to remove from the end-product because of their similarity to the intended species. bYlok technology relies on adjustments of the position of one of the disulfide bridges, which greatly favors the formation of a correct heterodimer species and delivers 95 percent correct heavy and light chain precision pairing with a mAb-like approach.

Generated bsAbs mimic parental antibodies in key characteristics such as yield, stability, immunogenicity, and functionality. In contrast to naturally occurring antibodies, bsAbs can simultaneously bind to two different types of antigen, which enables precision targeting, higher potency, and reduced clinical resistance. The biologics pipeline has been evolving, and a total of 273 bispecific molecules have successfully entered the clinic since 2001. Lonza developed its bYlok technology in response to the current market-wide challenge to design, develop, and manufacture bsAbs molecules at scale without the added implications of cost and time to market. The platform addresses technical limitations through a broadly applicable process, paving the way for the production of next-generation modern medicines.

FORESIGHT PRO CHROMATOGRAPHY COLUMNS, CHT CERAMIC HYDROXYAPATITE

Prepacked columns to support biomolecule purification

Produced by Bio-Rad Laboratories

Foresight Pro CHT prepacked columns support downstream process-scale chromatography applications across different stages of biological drug development and production. This includes a wide variety of purification and polishing applications for vaccines, monoclonal antibodies, and recombinant proteins.

The columns are prepacked with CHT ceramic hydroxyapatite media, a rigid mixed-mode support with unique separation properties used for the purification of biomolecules. The columns are available in a range of diameters and bed volumes, and manufactured in a controlled ISO Class 7 cleanroom and, thus, are GMP ready. Bio-Rad says that the columns deliver consistent performance and eliminate the need to pack, qualify, and validate the columns – and can be used for both early phase and manufacturing scale processes.

GIBCO CTS XENON ELECTROPORATION SYSTEM (XENON SYSTEM)

A customizable, scalable electroporation system for GMP-compliant cell therapy manufacturing

Produced by Thermo Fisher Scientific

Featuring programmable, flexible electroporation conditions, the CTS Xenon Electroporation System allows cell therapy developers to optimize a variety of hard-to-transfect cell types and payloads. Users can optimize multiple electroporation conditions simultaneously and identify the best electroporation conditions for unique cell and payload combinations. Once the ideal protocol has been identified, the system can be configured to a clinical manufacturing mode. The system has been specifically designed to enable an easier transition from the bench to the clinic.

Over 1,000 cell and gene therapy candidates are in clinical trials, which means there will likely be demand for pharmaceutical services that outstrip supply. The Gibco CTS Xenon Electroporation System helps researchers overcome manufacturing challenges to bring cell therapies to more patients. Using the modular Xenon System for nonviral gene modification enables time-consuming processes such as cell expansion, to be decoupled from rapid processes, such as gene delivery, improving facility and equipment utilization, and reducing the capital investment required.

KORUS

Cleaner cell populations through elutriation

Produced by Invetech

Korus is a closed system for autologous cell therapies that features elutriation and cell wash using gentle counterflow centrifugation. The system delivers purified cell populations for downstream processing development and commercial manufacturing, which Invetech says results in better overall process performance through higher recovery and purity of target cells. According to the company, there is supporting data demonstrating improved manufacturing performance compared to samples prepared by standard washing.

The double rotor centrifuge means that Korus can produce a full leukopak in one run, enable developers to accelerate clinical development. The input volume range of 25 mL to 5L and efficient run times also enable developers of autologous therapies to use the system from process development through to commercial manufacturing. Korus elutes lymphocytes to high purity levels, resulting in downstream performance improvements, such as greater Dynabead cell selection recovery and fold expansion (compared with standard washing protocols). And that reduces the impact of starting material variability, contributes to higher manufacturing yield, and reduces the risk of batch failure – all contributing to potential reduction in the cost of goods for future therapies.

PIN MILL PMV-320

Milling/micronizing platform that renders product ignition or explosion impossible

Produced by Frewitt Engineering Works

From potent APIs to fuels and many other powder ingredients, numerous products are susceptible to explosion, oxidation, and heat damage because of the kinetic energy required for milling products to the necessary particle sizes. Potent APIs can also endanger employees during handling. Manufacturers are therefore obliged to install containment measures. With the Pin Mill PMV-320, the entire milling process takes place in a vacuum (negative atmosphere), depriving products of sufficient air to ignite, heat, or oxidize. The negative pressure atmosphere enables processes to be contained easily, without costly and complex security measures. Moreover, the process – despite turning at speeds exceeding 200 m/s – is almost silent, which also enables users to forego hearing protection.

With a turn-key solution that does not require large amounts of nitrogen gas to mitigate explosion risk, Frewitt claims that the system will result in increased safety, while also helping preserve the active properties of medications by avoiding heat and oxidation.

QUANTUM FLEX CELL EXPANSION SYSTEM

An automated and functionally closed cell expansion system

Produced by Terumo Blood and Cell Technologies

Quantum Flex allows advanced therapy developers to complete their early process development on the same platform that they'll use for full-scale manufacturing, as well as create a cell culture environment in which cells thrive. The bioreactor platform provides optimal conditions for cell expansion with built-in advanced software to ease the deployment of protocols to multiple systems. Everyone from early and late stage researchers to commercialized developers will have access to the highest quality raw materials. The platform has the flexibility to progress autologous and allogeneic applications, as well as viral vector and exosome production, across multiple bioreactor sizes.

The system incorporates Terumo BCT's hollow-fiber perfusion technology, which provides a cell culture environment where cells have continuous access to fresh media, waste removal, and gas exchange, which ensures optimal conditions for expansion. And the software supports cGMP compliance, with user authentication, batch records, and fleet management features, allowing for easy deployment of protocols to multiple systems.

SKILLPAK BIO AND OCTAVE BIO

A bench-scale multi-column chromatography system with bespoke columns

Produced by Tosoh Bioscience

Octave BIO is a comprehensive and versatile multi-column chromatography (MCC) system with a modular design and added functionalities that support a range of process scales, implementations, and applications, including continuous purification. Notably, MCC technology enables process resin and buffer savings, among other benefits.

Alongside Octave BIO, the company has also launched SkillPak BIO, a set of pre-packed columns designed with standard shorter bed heights optimized for the fast flow rates and short residence times of MCC. Tosoh Bioscience has launched the two products together to offer a holistic approach to intensifying and optimizing purification steps, ultimately hoping to help companies reduce operating and capital costs while improving efficiency – both prerequisites for lowering biologic drug costs for patients.

THERMO SCIENTIFIC DIRECT MASS TECHNOLOGY MODE

Simultaneous charge detection for analysis of previously unmeasurable analytes

Produced by Thermo Fisher Scientific

By equipping the Thermo Scientific Q Exactive UHMR Hybrid Quadrupole-Orbitrap mass spectrometers with charge detection, Thermo Scientific Direct Mass Technology mode enables direct mass determination of hundreds, or even thousands, of individual ions in a single spectrum. This capability allows laboratories to measure mass for complex heterogeneous mixtures of multiple charged components, and unlock new insights into proteoforms, biotherapeutics, and next-generation drug modalities.

According to the company, the technology enables investigations that were once unachievable – from resolving heavily modified proteoforms to revealing small changes in large antibody-drug conjugate complexes. In short, the solution provides direct, accurate mass determination to help decipher protein complexes and biotherapeutics that are too complex to resolve with conventional methods.

TRANSGENE PLASMID ENGINEERING SERVICES

An engineering service for custom viral vector manufacturing

Produced by Polyplus

Polyplus' Transgene Plasmid Engineering services can deliver a fully customizable, scratch-engineered plasmid in just two weeks. The plasmids are assembled de novo from a library of DNA bricks, removing the use of standard backbones that contain undesired DNA sequences. An online plasmid portal (D-Zyvec) is used to draw the plasmid and model the design, engineering, and selection based on the preferred delivery of the gene of interest used in gene therapies. Once the plasmid is drawn, Polyplus' experts evaluate feasibility, enhance design, and deliver best-in-class plasmids for the process. The plasmids can be used alone or as a complement to reagents and kits.

The service was introduced to help the viral vector industry optimize process economics for advanced therapy manufacturing and enable customers to achieve more ambitious time to market goals. Operators can design and optimize their transgene before transfection in producing cells for viral vector production, ensuring better process results and speeding time to market.

ZENO SWATH DIA

Significant sensitivity gains to MS/MS data acquisition

Produced by Sciex

Combining the sensitivity of Sciex's TOF 7600 system with the dynamic range of the Zeno SWATH DIA enables quantification of up to double the number of cell and plasma proteins than traditionally possible – a significant step-change that can be applied even on low abundance species. Sample loads start at 10 ng with run times shortened to approximately 5 min, allowing large-scale biomarker studies to run as routine projects in a matter of weeks, without compromising the depth of proteome coverage. This reduction of time over traditional SWATH DIA is further amplified by higher quality data.

The sensitivity of Zeno SWATH DIA means large numbers of proteins can be quantified from significantly smaller sample loadings. Lower sample loads reduce cost in large-scale studies, minimize sample consumption from in vivo models during drug development, and create opportunities for large population-scale sample collection methods. The technology is designed to help researchers discover more potential biomarkers in the development of clinical tests and in the discovery of new therapies. The ability to quantify large numbers of lesser abundant, previously undetectable proteins means more potential biomarkers can be taken through to verification.

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Important biomarkers are often lowly abundant, appearing below the limit of detection of common analysis tools such as quantitative PCR (qPCR). The sensitivity and precision of Droplet Digital™ PCR (ddPCR™) technology gives scientists the power to detect and quantify nucleic acids in liquid biopsy samples for rare mutation detection, mutation monitoring, and other oncology research applications. To unlock even more capabilities, Bio-Rad Laboratories recently released the QX600™ ddPCR System.* This technology:

- Delivers more answers per sample – Advanced six-color multiplexing enables clear discrimination and quantification of up to a dozen biomarkers per well. This conserves resources, improves efficiency, and reduces reduces the need to split precious samples.
- Maximizes clinical research impact – Scientists can obtain better data than ever before with the ultra-high precision, sensitivity, and reproducibility of the QX600.
- Accomplishes more with a single instrument – This highly versatile platform can quantify SNPs and structural variants, characterize methylation, perform RNA expression analysis, and more.
- Simplifies clinical research laboratory logistics – Same-day turnaround time, simple workflows, and intuitive data analysis lower the burden on laboratory teams, reducing the need for specialized training and freeing up time to answer other important scientific questions.

Hundreds of publications have already demonstrated the robust utility of ddPCR technology for translational research in both academic and commercial settings. In particular, ddPCR assays have proven ideal for serial monitoring that allows researchers to track disease progression and identify disease recurrence.

When combined with broad characterization methods such as next-generation sequencing (NGS), the QX600 ddPCR System is a powerful and versatile instrument that is part of an ideal precision medicine workflow. Its sensitivity, precision, versatility, and ease of use make it an invaluable tool for researchers working to understand and treat cancer and other diseases.

Visit www.bio-rad.com/qx600 to learn more and find ordering information

*Research Use Only. Not for use in diagnostic procedures.


FREWITT

THE PIN MILL PMV-320: PROTECTING USERS AND APIS

The extreme kinetic energy often required to mill products to the required particle sizes can make many products – from potent APIs to fuels – susceptible to explosion, oxidation, and heat damage. In addition, potent APIs can also endanger those who become exposed, obliging manufacturers to install expensive containment measures to protect employees.

By employing a sequence of sensors, vacuum pumps, and valves, the patented Pin Mill PMV-320 performs the entire milling process continually in a vacuum (negative atmosphere). Sensors send signals to the valves and pumps ensuring that they run in proper sequence to both maintain a vacuum within the machine, and to ensure that powder metering, powder milling, and powder discharging run in a continuous manner. This milling platform not only guarantees the highest levels of safety for user and product, but also the most cost-efficient process available for high-throughput, ultra-fine micronization.

A patented process that puts user safety first

Frewitt's unique Pin Mill PMV-320 is easy to use, affordable, and checks all the boxes in terms of user safety – protecting users against explosion, contamination, and harmful noise – even though the mill spins at speeds exceeding 200 meters per second, it is almost silent, allowing users to forgo hearing protection. Our patented milling process boosts safety, while reducing cost and complexity. Other technologies in the market can consume massive amounts of nitrogen to make their processes inert, which not only necessitates vast, complicated gas management systems to manage and evacuate the gas, but also poses a serious potential hazard to operators.

Safety without sacrifice

Fortunately, the many safety benefits of milling in a vacuum are not at the expense of process performance or API integrity. In fact, the negative pressure atmosphere of the PMV-320 allows the process to be contained easily and protects the API being milled from heat and oxidation. And because the product is protected from long residency times and repetition in the milling process, the API properties are better conserved, resulting in increased stability.

In summary, the Pin Mill PMV-320 protects users, protects API, facilitates a much cheaper, simpler physical plant set-up – and, in many cases, can replace jet mills and air classifier mills while requiring a much smaller installation area.

Learn more at https://youtu.be/z8igkZ7hGaQ

An End-to-End Cell & Gene Therapy Development Partnership

Cell and gene therapies are continuing to gain popularity, with 15 now FDA approved[1] and hundreds more in development. While these treatments are promising, managing safety and effectiveness in patients is complex. Around the world, groups ranging from drug discovery, development, and manufacturing to clinical laboratories are using Bio-Rad's Droplet Digital™ PCR technology as a reliable and scalable solution to myriad workflow challenges.

In Process Testing

WHY CELL & GENE THERAPY SCIENTISTS TRUST *ddPCR*....

- Plasmid Integrity
- Viral Titer
- Transgene Copy Number
- Transgene Expression

Key Benefits

- Precision
- Accuracy
- Inhibitor Tolerance/ Sensitivity
- Multiplexing

Goals: CMC submissions, efficient and scalable process development

Final QA/QC

WHY QA/QC SCIENTISTS TRUST *ddPCR*...

- Residual DNA
- Viral Titer
- Mycoplasma Detection
- Transgene Copy Number

Key Benefits

- Accuracy
- Sensitivity/ Specificity
- Time to results

Goals: Reliable assessments of purity, potency and safety

Clinical Research

WHY CLINICAL RESEARCHERS TRUST *ddPCR*...

- Serial Monitoring
- Biodistribution
- Dose Response Evaluation

Key Benefits

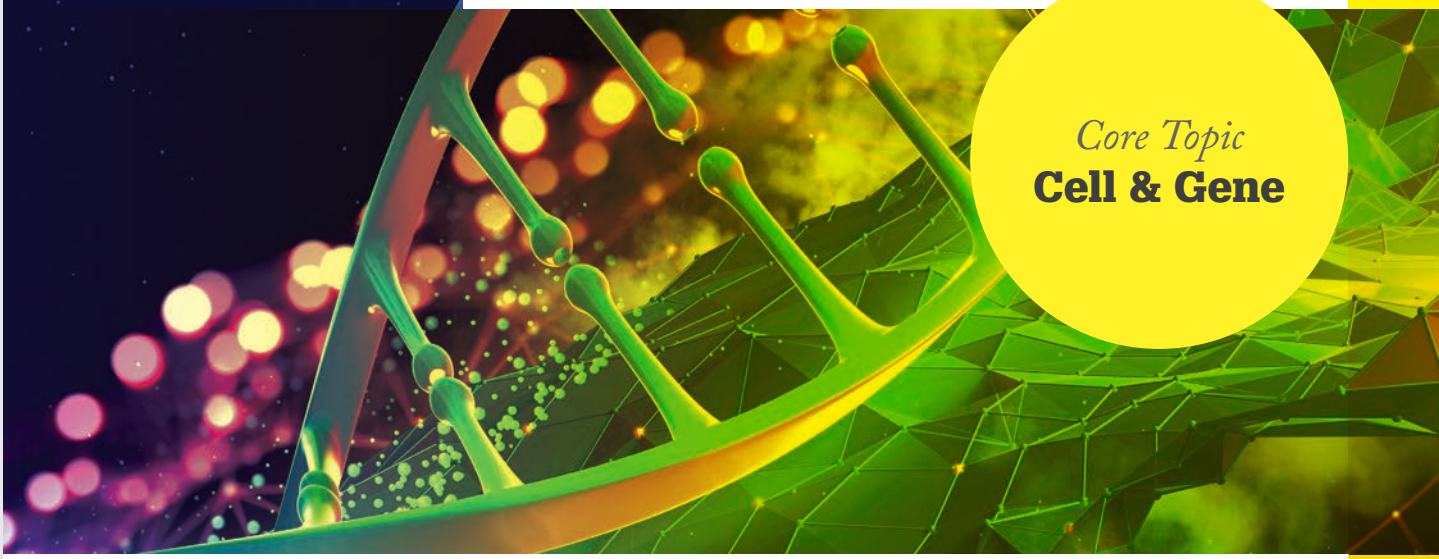
- Accuracy
- Sensitivity
- Precision

Research Use Only

Goals: Effective evaluation of cell & gene therapies in patients

Explore Bio-Rad's end-to-end solutions for developing and manufacturing cell and gene therapies at www.bio-rad.com/cgt-resources

1. Center for Biologics Evaluation and Research. Approved cellular and gene therapy products. Retrieved July 01, 2021, from https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapyproducts/approved-cellular-and-gene-therapy-products



Core Topic
Cell & Gene

Abeona advances. US company Abeona Therapeutics has enjoyed a double helping of good news. First, the company's EB-101 cell therapy for "butterfly disease" (recessive dystrophic epidermolysis bullosa) has bounced back from a 2019 FDA clinical hold to present phase III evidence of meeting co-primary endpoints of the VIITAL study (achieving 50 percent wound healing and reduced pain). Second, Abeona has raked in $35 million through sales of shares, which will be used to keep the company running through to late 2024. Currently, patients with the dystrophic form of epidermolysis bullosa have a life expectancy of 30 years.

Relapse/recovery. New findings in New York, by way of a joint project between Mount Sinai and the Memorial Sloan Kettering Cancer Center, have shed new light on options for treating patients who suffer a cancer relapse after receiving CAR T-cell therapy, and then have no strong options to turn to. The researchers applied a range of different therapies to relapsed patients who had received BCMA-directed CAR T, and found that treatments that engaged with T cells worked best against the cancers for the longest period of time. These treatments included bispecific antibodies and other forms of CAR T-cell therapy.

Relapse as a material question. A study from the Children's Hospital of Philadelphia offers insights into how poverty affects American children treated with CD19 CAR T therapy. The researchers found that poverty had no significant effect on complete remission or hazard of death rates, but did find that patients from poor neighborhoods are at greater risk of relapse than their wealthier counterparts. The team has recommended further investigation of multicenter outcomes and access disparities. According to Save the Children and The Center for American Progress, around one in seven children in the US live in poverty – with the worst hit groups being black and latin minorities, and families living in rural areas.

Fine then! A recent decision by the US Supreme Court has dealt good news to Gilead, and bad news to Bristol Myers-Squibb. Just over one year ago, a federal appeals court overturned a pro-BMS verdict, scuppering the company's attempt (through BMS' subsidiary, Juno) to sue Gilead (through Gilead's subsidiary, Kite) for $1.2 billion for (allegedly) copying its own patented CAR T therapy to help create and commercialize Gilead's Yescarta. Since then, the case climbed the American legal ladder all the way to the Supreme Court, who simply declined to hear it. To use the Court's own six words: "The appeal is dismissed as moot."

IN OTHER NEWS

$487 million deal sees Eli Lilly purchase inner ear gene therapy specialists Akouos, acquiring its portfolio of AAV-delivered therapies

Galapagos drops 200 staff, kidney disease program, and remnants of fibrosis program; aims to focus on CAR T for immunology and oncology

Charles River announces plans to expand in Memphis' Bluff City; will add nine cell therapy processing suites, bringing total to 23

Mouse research in Rice University, Texas, shows immune profiling of AAV response can identify B cell-specific targets that enable vector re-administration with minimized immunosuppression

Small data sample from Intellia first-in-hunan study indicates that gene editing candidate NTLA-2002 may serve as functional cure for hereditary angioedema

Less Than 5 Percent Human Effort: Thoughts on the Role of Automation

We all know that automation can reduce human labor, but how else can it make economically viable cell and gene therapies a reality?

By Dalip Sethi, Director of Scientific Affairs, Terumo Blood and Cell Technologies

"Automation" means different things to different people. To me, this word primarily means "tasks completed with minimal human interaction" – less than 5 percent, to put a figure on it. Under automation, more than 95 percent of the tasks at hand are completed by a non-human system, especially tasks spanning over multiple days such as cell culture. An automated device should be able to carry out an assigned protocol repeatedly without requiring human assistance.

There is no need to explain all the benefits that automation can offer to modern industrialized economies, nor is there any need to discuss the basic benefits that automation can offer to cell and gene therapy – numerous iterations of those articles already exist.

However, it is absolutely worthwhile to take stock of some of the most important recent advances in cell and gene therapy automation.

First and foremost, I am excited about my company's new cell expansion platform, Quantum Flex. But this year, a new release from Invetech also caught my eye – a device for cell washing and concentration. Both innovations received significant attention – but not as much attention as the advances in the science of cell and gene therapies overall. Approvals of CAR T therapies, for example, always receive fanfare far louder than the release of any automated wonder-tool.

Is this a problem? I don't think so. Technology and its providers are the enablers of science. The scientists and physicians working on the therapies will always lead the way. I see no problem with that aspect of the status quo. Cell and gene therapy has shown high response rates in the clinic, and so as a technology provider I am quite content to be one of the people who paves the road for scientists and physicians to progress their discoveries towards commercialization.

The past is gone

In the past, cell and gene therapy companies borrowed technologies from the blood and transplant spaces, and began implementing them in their own field to meet new unmet medical needs. The goal was simply for the cell and gene field to function. Now, technologies are being specifically designed for the cell and gene therapy market. As the field matures, the transition from borrowed to "native" automated technologies is one aspect of the new era.

However, the big barrier to fully entering that era is cost. It's fairly common knowledge that labor constitutes a major proportion of the cost weighing down cell and gene therapy, and it's true that automation has been driving down costs by cutting labor out of the equation since the 18th century. The less obvious point I'd like to make is that automation is not the only means of reducing labor costs in cell and gene therapy. If we keep our focus on the field's non-human entities – on machines and the buildings that house them – then we can look to a one-off investment in an efficient manufacturing system as one way to bring down running costs. The initial construction may not be cheap,

but over time it will pay for itself.

If we also look at the humans who turn the wheels of cell and gene therapy, we need to consider their career ambitions and the economic dynamics of the jobs market that they are navigating. The supply of highly skilled and educated scientists and technicians is far below demand, which has produced a highly competitive market. Individual workers have ample opportunities to boost their salaries by jumping ship, and companies are highly incentivized to catch them before they even hit the water, so to speak. Everyone is taking from everyone else, which increases running costs. If better training and workforce development can draw more talent to the field and strengthen the incentives that connect employees and employers, perhaps those costs can be reduced over time.

Humans vs machines: a false dilemma

Using the right automated devices can boost the production and scale of the production process too, thus reducing the cost burden without necessarily shrinking or growing the workforce. In the case of CAR T-cell therapy manufacture, the possibilities are particularly exciting. If you want modified CAR T cells to grow, you have to support their special needs: the right cell culture environment and the right cytokines. You can meet these needs in bags, in flasks, and in containers – but I would recommend growing them in a hollow fiber.

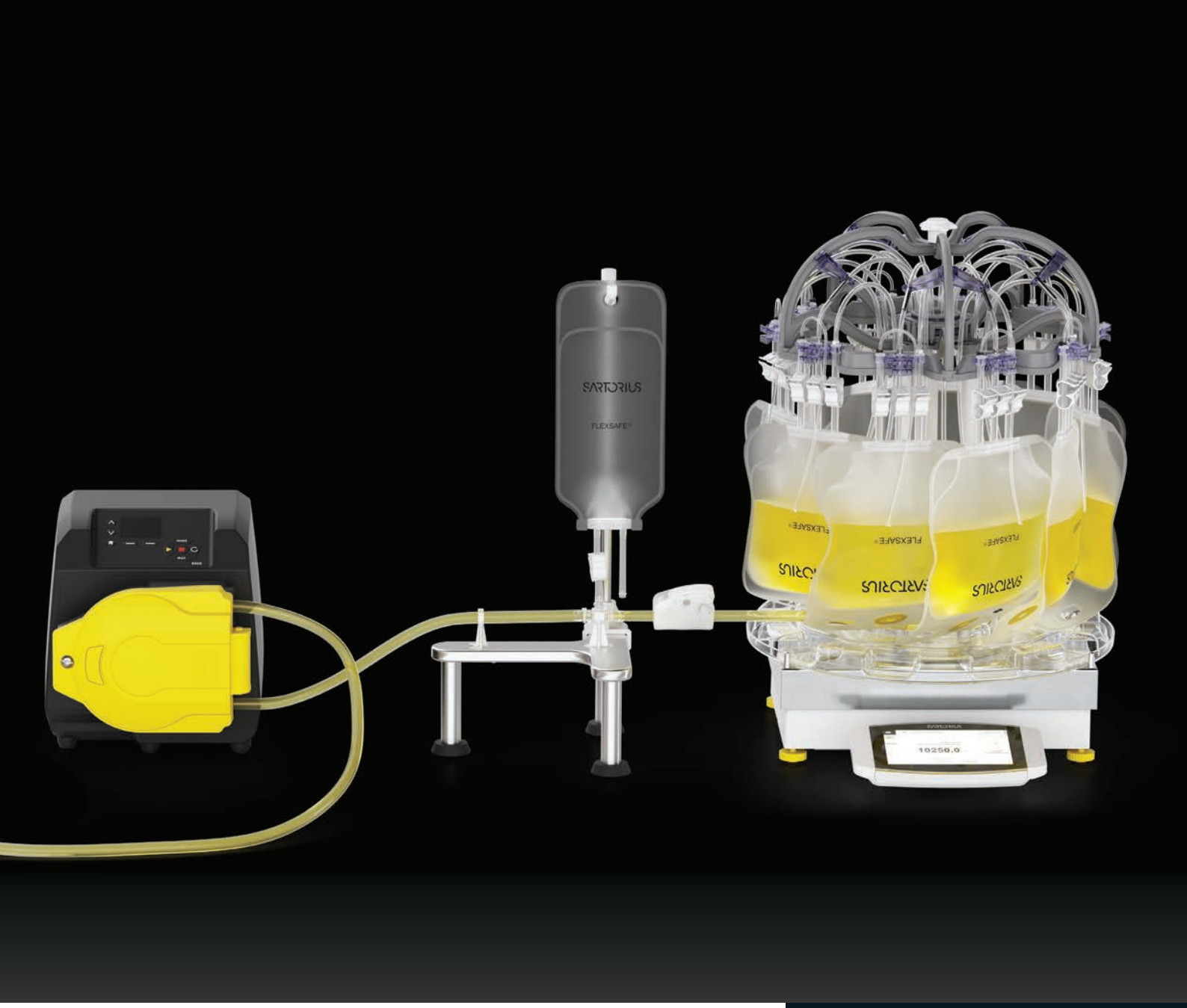
Let's say you need to grow 2 billion cells. If you choose to do this inside a bag, you will need to add a high volume of expensive cytokines and nutrients, because there is no membrane-based separation inside that bag. Hollow fiber bioreactors create a dual chamber system – in simple terms, think of it as a straw made up of a semi-permeable membrane that allows only a specified size of molecules through its pores. In essence, it allows you to keep the cells inside the straw and provide them with what they need. The membrane allows small molecules, such as glucose, lactate, oxygen, and CO2 to pass freely, allowing the control of the cell culture environment. The large molecules – such as the expensive cytokines and media components – can be kept in the cell compartment, intra-capillary (IC), side. One practical upshot of this is that the total volume of complete media you need for CAR T production may decrease, along with the cost.

Another practical benefit of applying the hollow fiber approach concerns time. The hollow fiber system demands a far lower number of seed cells than does a bag culture. This can save precious time that would otherwise be spent on jumping hurdles during the extraction of sufficient cell samples from the patients.

The future is normal

I would like to point out that hollow fiber devices are not new technology. When they were first released around 2011, they offered a very futuristic approach. But now – in a sense – that future is here and normalized. Numerous studies have demonstrated the ability of hollow fiber technology in the expansion of a multitude of cell types. Looking ahead to the next ten years, we can get a sense of what new normalities the next wave of automated cell and gene technology could introduce.

Right now, we are seeing a great deal of work on biosensing tools for monitoring and altering the cell culture environment. While biosensors are currently adopted at many cell manufacturing levels, we are just beginning to understand the applications of machine learning and feedback circuits in the field of cell and gene therapy. At present, we leave cells in incubators, and we monitor their environment, but we don't try to change that environment. As practices around cell culturing evolve, we should see the emergence of means to more closely analyze the key markers – such as glucose, lactate, oxygen, CO2, and pH. With enough data, machine learning models may be able to train the systems via feedback loops to optimize the cell cultures. Right now, we don't have enough data – and even in five years we may still be discussing the possibilities rather than enacting them. But I do believe this is an area to keep a keen eye on – an area from which great things are certain to emerge. In that sense, it has a great deal in common with the story of cell and gene therapy so far.



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Core Topic
Bioprocessing

Award for Ebola treatment. Regeneron's Ebola treatment Inmazeb (a cocktail of atoltivimab, maftivimab, and odesivimab-ebgn) has been crowned "Best Biotechnology Product" of 2022 by the Galien Foundation. The drug, approved by the FDA in 2020, was made using the company's VelociSuite technologies, which help accelerate antibody target discovery and validation. The cocktail neutralizes the Ebola virus by "blocking the virus from entering into host cells via the glycoprotein and/or enables antibody-dependent effector function by bringing in other immune cells to target infected cells, which is a way for an antibody to get extra help from the immune system in order to clear infected cells from the body."

Delaying diabetes. Provention Bio has received FDA approval for Tzield (teplizumab-mzwv) for delaying the onset of stage 3 type 1 diabetes in adults and children over the age of 8 years old. In trials, the anti-CD2-directed antibody was able to delay onset of stage 3 type 1 diabetes by around 25 months. "It cannot be emphasized enough how precious a delay in the onset of Stage 3 T1D can be from a patient and family perspective; more time to live without and, when necessary, prepare for the burdens, complications and risks associated with Stage 3 disease," Ashleigh Palmer, Co-Founder and CEO of Provention Bio, said in a statement.

GSK's bad news. GSK had once hoped it had a potential blockbuster in hand with otilimab, but the ContRAst phase III study results are in – and it's not positive. The drug was being tested in rheumatoid arthritis patients who had an inadequate response to or who could not tolerate available treatments. The study results show that it does work better than placebo at reducing symptoms in patients who'd had an inadequate response to methotrexate and conventional DMARD drugs. However, the drug did not demonstrate a statistically significant response versus placebo in patients with inadequate response to biologic DMARDs and/or JAK inhibitors.

Warning shot. BMS's Abraxis Bioscience has received an FDA warning letter. The manufacturer experienced multiple media fill failures between April and October 2021 when simulating the aseptic process used to fill Abraxane (nab-paclitaxel). According to the FDA, the company failed to "sufficiently" evaluate and remedy the situation – and batches potentially affected by the failures were released in December 2021. In the letter, the FDA said, "Investigations into the following media fill failures were inadequate in that they lacked sufficient rigor in determining root causes and scope of impact after the media fills revealed serious non-sterility risks in your aseptic process operations."

IN OTHER NEWS

BioNTech acquires manufacturing facility from Novartis Singapore that will serve as BioNTech's regional headquarters and Singapore's first mRNA manufacturing facility

New cell line development technologies have launched; Aragen's optimized RapTr 2022 and ProBioGen and Thermo Fisher Scientific's Gibco Freedom ExpiCHO-S

Pfizer says bivalent RSV vaccine candidate saw positive results in study; company preparing to submit BLA to FDA by the end of 2022

EnteroBiotix partners with Imperial College London for R&D into microbiome therapeutics for blood cancer; plans include phase IIb trial of EBX-102 for bone marrow transplants with blood cancer

Cytiva opens 11,500 square foot Cell Culture Center of Excellence at its Marlborough, Massachusetts site

Fresh Hope for ADC Development

Historic challenges in ADC development have not thwarted the hopes of some players

The potential benefits of antibody-drug conjugates (ADCs) to cancer patients have been hyped by the pharma industry for many years, but breakthroughs have been slow. Now, with approvals occurring faster and more frequently, we could be witnessing a burgeoning trend.

Lonza operates HPAPI suites in Visp, Switzerland and Nansha, China, that can manufacture cancer-killing payload-linkers at scale. Here, Giovanna Libralon, Senior Director, Commercial Development – Small Molecules, and Iwan Bertholjotti, Senior Director, Commercial Development and Strategic Marketing – Bioconjugates, share their thoughts on the present and future of ADC development.

The industry has been debating the promise of ADCs for many years; are we finally on the cusp of a significant trend in this field?

Giovanna: It is true that it has taken time for the pharmaceutical industry and regulatory authorities to understand the potential of ADCs. The first ADC was approved in 2000, but it took until 2011 for the next one to get clearance, with further approvals in 2013 and 2017. However, the numbers have quickly accelerated in the last four years. From 2018 to 2021, seven ADCs were approved by the FDA, suggesting a rapid acceleration in both understanding and use cases. This is reflected in the high activity in development pipelines too, on top of the dozen anticancer ADCs already in the market.

Iwan: I would say that we are no longer on the cusp of a trend but have passed the stage where the only way is up. The innovators bringing these drug products to the clinic are no longer just big pharma companies – although they do still dominate the current approval list for ADCs. Many are now being developed by small biotech companies. From preclinical evaluation to commercial launch, these businesses are almost entirely reliant on outsourcing partners to produce material.

Why is oncology such a key area for ADC development?

Iwan: Many cancer therapies on the market cause damage to healthy tissue outside of the therapeutic area. This off-target activity results in adverse side effects, adding difficulty and discomfort to a patient's condition. The precise nature of the ADC – enabled by the antibody as well as the HPAPI – decreases these side effects and improves the therapeutic effect in comparison with standard care, which is exactly what drives the demand for anticancer ADCs.

Giovanna: The selectivity of ADCs – enabled by the antibody that delivers the payload to cancer cells expressing the target antigen – allows the development and application of payloads that cannot be administered systemically because of their high toxicity. The combination of this high selectivity, driven by the antibody, and the extreme potency of the small molecule drug explains why ADCs are a fast-growing cancer therapy.

How has the development and manufacture of ADCs improved in recent years? What do you think have been the key milestones?

Iwan: On the biologics front, the commercial manufacture of monoclonal antibodies has become more streamlined as advancements in technology and regulatory understanding evolve. Different conjugation technologies and payloads passed the important cliff to get market approval representing a proof of concept. In addition, novel conjugation technologies, such as site-specific conjugations, have also emerged. Different payloads will always further diversify the application of bioconjugates/ADCs. At Lonza, we've seen a huge variety in modalities, including polymer, peptide, oligonucleotide, chelators for radiolabelling, and the connection of different microbial derived serotypes for vaccines, alongside other established high potent payloads.

Giovanna: Although every component of the ADC is essential to its therapeutic activity, the payload is the one that kills cancer cells. These payloads are almost always small molecule HPAPIs. Carefully selecting the right one is incredibly critical as it needs to have the desired clinical outcome, but not be so toxic that the side effect is unmanageable. And now we're seeing a rise in the ADC pipeline with a strong diversification of payloads with new mechanisms of action in the preclinical phase.

What are the limitations of ADC development right now and how do you think therapies will evolve in the future?

Iwan: There are many new ADCs under development in the preclinical stage. With that, I don't really see limitations but exciting potential for a continuous flow of new ADCs into the clinic and market. As there are a lot of unmet needs for difficult to treat diseases such as cancer, there is a healthy competition between different technologies and modalities. Whatever concept improves the lives of patients suffering from these conditions will be a success, and I expect ADCs will play a relevant role in that.

Giovanna: I'm optimistic about how these therapeutic areas will diversify outside of oncology in the next couple of years, as several ADCs in the pipeline already address musculoskeletal conditions and autoimmune diseases.

Positive Opinion for Regeneron's Libtayo

Israel Lowy, SVP, Translational and Clinical Sciences, Oncology, at Regeneron Pharmaceuticals, explains how a positive CHMP opinion can become good news for cancer patients

What factors do you think contributed to a positive EMA CHMP opinion for Libtayo (cemiplimab)?

The CHMP's recent positive opinion is based on data from the global phase III EMPOWER-Cervical 1 trial, which showed that Libtayo significantly extended survival compared with standard-of-care therapy in patients with advanced cervical cancer regardless of PD-L1 expression level and histology (1).

The trial's primary endpoint of overall survival was met, with Libtayo reducing the risk of death by 31 percent in the total population and 27 percent in the squamous cell carcinoma population compared with an investigator's choice of chemotherapy. Additionally, treatment with Libtayo prolonged progression-free survival by 25 percent compared with chemotherapy and a greater percentage of patients treated with Libtayo achieved an objective response than those treated with chemotherapy.

These results demonstrate that Libtayo has the potential to provide new and valuable treatment options to people living with advanced cervical cancer in Europe.

What's the next step for EU officials on its path to full approval?

Libtayo's availability may vary in each country based on national and regional reimbursement policies. Following the positive CHMP opinion, the European Commission will make a final decision on the marketing authorization application for Libtayo in advanced cervical cancer. We expect that decision in the coming months.

Were there any negative side effects?

No new Libtayo safety signals were observed in the phase III trial. Among adverse events (AE) observed in 10 percent or more patients in either group, Grade 3 or higher AEs that occurred more often in the Libtayo group (n=300) than in the chemotherapy group (n=290) include:

- Urinary tract infection (5 percent Libtayo, 3 percent chemotherapy).
- Back pain (1 percent Libtayo, <1 percent chemotherapy).
- Asthenia (2 percent Libtayo, 1 percent chemotherapy).
- Arthralgia (<1 percent Libtayo, 0 percent chemotherapy).
- Pyrexia (<1 percent Libtayo, 0 percent chemotherapy).

How do you expect Libtayo to benefit cancer patients, particularly women?

Despite recent advancements in the prevention and treatment of cervical cancer, there remain limited options for people with recurrent or metastatic cases – especially those who do not express PD-L1. We believe that Libtayo has the potential to make a meaningful difference for patients battling this difficult-to-treat cancer.

Science has the power to change the trajectory of people's lives – including those with advanced cervical cancer, a disease that has historically had limited treatment options. In recent years, following the availability of the HPV vaccine, there has been a significant decrease in the incidence of cervical cancer, but it remains a leading cause of death in women worldwide (2). The CHMP's recommendation to approve Libtayo for advanced cervical cancer shows that, although there is still work to do, progress is being made.

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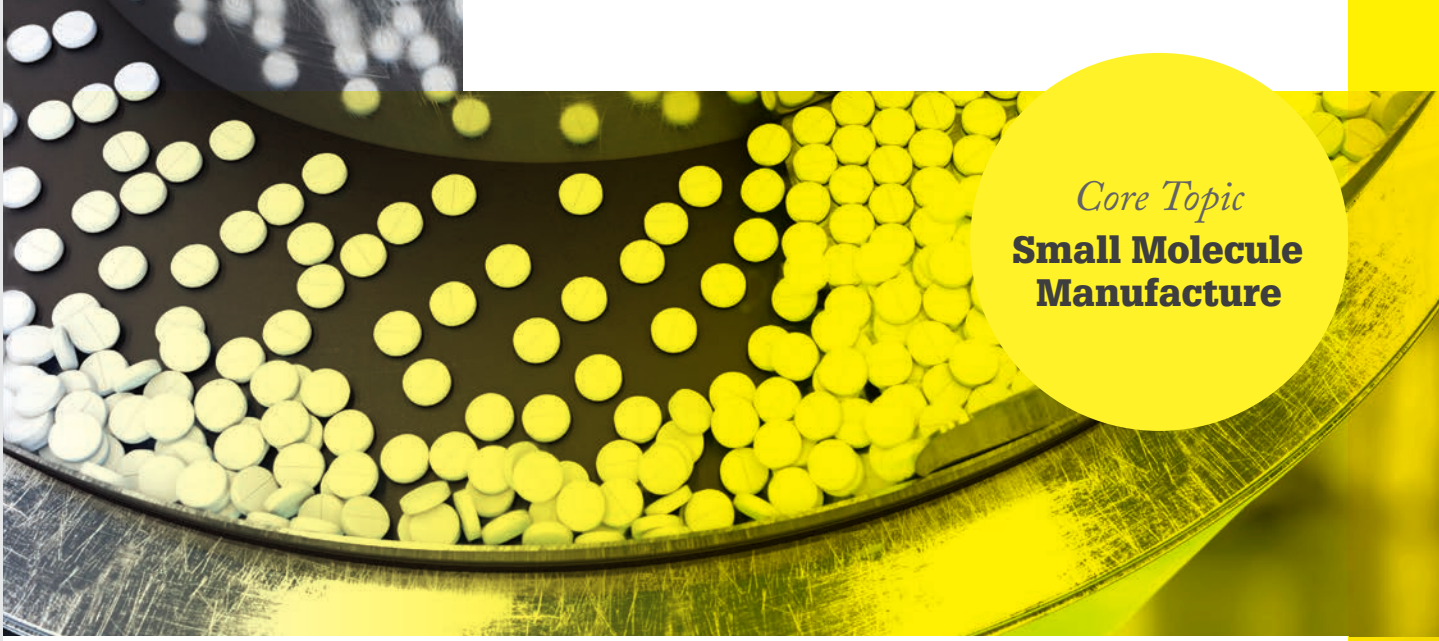


Core Topic

Small Molecule Manufacture

Revocation or Provocation? US-based conservative law consortium Alliance Defending Freedom, on behalf of the Alliance for Hippocratic Medicine, is suing the FDA to revoke its approval of the abortion medicine mifepristone (Mifeprex) on the grounds that the agency has been "running roughshod over the law and science" for decades. The group claims that the FDA was pressured by the Clinton administration into disregarding the safety of the drug and ignoring potential adverse events in adolescent women. Originally approved in 2000, a 2016 updated approval "modified the gestational age up to which Mifeprex has been shown to be safe and effective," according to the FDA.

Think Small. Scientists from the Berlin Institute of Health at Charité, in collaboration with counterparts from the University of Cambridge, have measured the amount of small molecules from blood samples of around 20,000 participants in two large population studies to investigate the influence of the genome, identifying regions linked to diverse metabolites. The researchers were able to demonstrate which changes in metabolism contribute to the development of diseases, including breast cancer. The study published in Nature Medicine is titled "Rare and common genetic determinants of metabolic individuality and their effects on human health."

Amazon Under Fire. Amazon.com has received a second Warning Letter after the FDA tested dietary supplements being sold on the site and "fulfilled by Amazon," and found APIs not listed on the product labels, including diclofenac – a non-steroidal anti-inflammatory drug (NSAID) that may cause increased risk of cardiovascular events and potentially fatal gastrointestinal damage – as well as dexamethasone and methocarbamol. The specific products cited by the FDA were "Artri Ajo King," "Artri King Reforzado con Ortiga y Omega 3," and "Ortiga Mas Ajo Rey," which now appear to have been removed from the online marketplace.

Raising the bar on AMR. A new report from ICMRA titled "Antimicrobial Resistance Best Practices" presents case studies on best practices developed in line with the coalition's 'One Health' approach that address antimicrobial resistance and antimicrobial use in humans, animals, and the environment. The best practices focus on regulatory flexibilities that help bring novel therapies to market, sales reporting of medically important antimicrobials for veterinary use, lessons learned from the COVID-19 pandemic, the restriction of non-prescription antibiotics, and the treatment recommendations for common infections in outpatient care, amongst others.

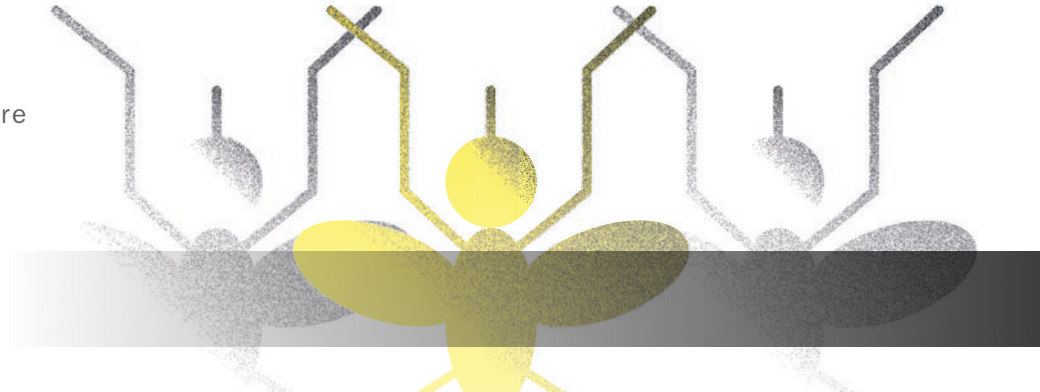
IN OTHER NEWS

University Hospitals and Case Western Reserve University study details cholesterol-lowering, orally administered drug that reduces PCSK9 levels in animal models by 70 percent

AstraZeneca and MSD's Lynparza (olaparib), in combination with abiraterone and prednisone or prednisolone, recommended for marketing authorization in the EU for metastatic castration-resistant prostate cancer

RedHill Biopharma announces positive in vivo results from pre-clinical study evaluating the effects of opaganib on radiation-induced hematologic and renal toxicity

Study commissioned by the Global Respiratory Infection Partnership and lozenge manufacturer Reckitt claims the high dependence on antibiotics to treat respiratory conditions is linked to antimicrobial resistance



Fighting the Resistance – to Malaria

Researchers examine how combination therapies for malaria lead to drug resistance

Malaria has played a long and enduring role in human history. The disease is thought to have first emerged hundreds of thousands or millions of years ago. Although our understanding of this parasitic disease has drastically improved as contemporary science has advanced, researchers are still faced with the quandary of developing relevant medicines and therapeutics against it.

Many medicines against malaria have been developed, but all have lost efficacy due to the parasites' ability to evolve and develop drug resistance. In the first decade of the 2000s, we saw the most widely used antimalarial drugs, the artemisinins, begin to lose their efficacy as well. The resulting dearth of treatment options has left patients and those at risk of contracting the disease – particularly those in low- and middle-income countries (LMICs) – in a vulnerable state.

When artemisinin first emerged as a treatment option in the 1990s, it was welcomed by some countries' national malaria programs. Commenting on the importance of the drug, Maciej Boni, Associate Professor of Biology at Penn State University, says, "A small series of clinical trials were carried out in southern Vietnam in the 1990s. Though few were familiar with the drug prior to this, the studies proved its potency." Eventually artemisinin-combination therapies were recommended by the World Health Organization in 2005

Today, artemisinin is the leading treatment for malaria, but artemisinin resistance is now common in southeast Asia and emerging in eastern Africa. To slow this phenomenon and protect as many patient lives as possible (and for as long as possible), appropriate drug monitoring will make all the difference. "Typically, resistance emerges very slowly and requires constant surveillance. This means that we need dedicated networks of scientists working to collect and genotype samples," says Boni. "By creating rapid and responsive surveillance networks, we can help improve treatment in endemic countries and facilitate communication between public health institutions and patients."

But good surveillance relies on an understanding of resistance evolution in artemisinin and the partner drugs used alongside it in many regions of the world. Along with colleagues at Penn State University, the University of Oxford, and Imperial College London, Boni has found that resistance to partner drugs also encourages early resistance to artemisinin. He says, "We were looking at the conditions that affect resistance evolution. The reason it was previously so difficult to discern was that the earlier stages of resistance occur slowly. Therefore, it is a challenge for public health systems to detect."

In particular, the team's research focused on artemisinin partner drugs piperaquine, amodiaquine, and lumefantrine. To varying degrees, malaria has already developed some resistance to these drugs, but Boni and colleagues found that, when partner drug resistance levels are high, artemisinin resistance evolves even more quickly than expected.

The discovery is only more proof, he explains, that further surveillance is necessary to manage antimalarial resistance. In doing so, public health bodies and other healthcare stakeholders will be able to more appropriately respond to resistance as and when it occurs. "If we take Rwanda as an example, we already see signs of artemisinin resistance. With good surveillance in place, we would have a better idea of when to start enrolling patients in trials for alternative artemisinin-based combination therapies and see if the new treatment approach allows them to clear the parasite."

Boni and his Penn State colleagues are now working in collaboration with the World Health Organization and in-country national malaria control programs to assess the current situation in Rwanda, Burkina Faso, and other countries, and to make projections of what the next five to 10 years might look like.

"It's hard to say what things will look like in five years," he says. "Just like weather reporters can provide a forecast for the next few days, but can't tell you with certainty what the weather will be like over the next month, we don't know precisely how the future of malaria resistance will pan out. That's why it's so important to start thinking about drug resistance management early."

But effective management requires good funding. The better access researchers and national programs have to funding, the easier it will be to establish and strengthen management systems. Boni says, "In the next 10 to 15 years, we need to see more funding channeled into this area. We've come a long way when it comes to malaria; 15 years ago, it was considered a neglected disease. Although funding has massively increased in the last two decades, which was the right course of action, we need more of it to see a bigger impact in patient lives. Imagine how far we can go with the right tools and resources in place."

Embracing Enzymes

To meet increasing global demand for more efficient and greener processes, environmentally friendly catalyst technologies are on the rise

By Ahir Pushpanath, Team Leader, Biocatalysis, at Johnson Matthey

As pharma companies grow more mindful of the environmental impact of their products and supply chains, chemists and engineers are turning their attention to increasing efficiency and reducing waste in API synthesis. One attractive solution relies on nature's catalysts – enzymes – which can be used as highly specific and selective "biocatalysts." Notably, biocatalysts follow many of the principles of "green chemistry", making them an attractive alternative to chemocatalysts.

So why aren't more companies embracing enzymes? Put simply, the entire workflow of biocatalysis – from sourcing, development, and optimization of an enzyme, to finally delivering a biocatalyzed process – is a complex, multidisciplinary affair. And that's why, for the pharmaceutical industry to fully leverage the power of biocatalysis, it's vital to tap into advances across the key areas of enzyme screening, engineering, immobilization, and bioprocessing.

With the growing complexity of pharmaceutical APIs, the demand for biocatalysts that are active towards novel, non-natural substrates has also increased. However, this is at odds with natural evolution, which has produced an impressive library of powerful yet substrate-specific enzymes. As such, many industrial reactions do not have a process-ready natural biocatalyst because the enzyme's active site is suboptimal for accommodating the desired substrate.

To overcome this hurdle, scientists developed an approach that mimics natural evolution in a laboratory setting by randomly mutating, screening, and selecting thousands of enzyme variants. Using "directed evolution", enzyme development scientists can incrementally address inherent hurdles, such as substrate scope, undesirable selectivity and process stability of the natural enzyme starting point. The importance of this technique for the pharmaceutical and wider chemical industry was recognized by the 2018 Nobel Prize in Chemistry – awarded to Frances Arnold.

Though directed evolution showcased the power of engineered enzymes for industrial biocatalysis, the iterative cycles required to deliver a final process-ready biocatalyst is not always compatible with drug development timelines. Additionally, drug development suffers from a high attrition rate, making the return on investment for designing a new biocatalytic route uncertain. Therefore, for more biocatalyzed processes to be realized, we first need to enhance biocatalytic solutions for all desired routes and shorten enzyme engineering timelines.

Although the enzyme engineering field is synonymous with Arnold's directed evolution technique, the mounting understanding of protein sequence–structure relationships has allowed for rational design to mature. Rational design approaches rely on computational analysis of sequence alignments and protein structure/dynamics to predict the exact changes required to elicit a desirable effect in the enzyme. The strategy has more success when prior structural and experimental data is available for the specific candidate enzyme or family of enzymes. Although still prone to high failure rate, if successful, enzyme development timelines can be drastically reduced.

At the intersection of both these methods is semi-rational design. By rationally and accurately predicting favorable "hotspots" on the enzyme structure through proprietary computational workflows but also allowing for randomness at hotspots, we can create a smart library that increases our chance of finding vastly improved enzymes in reduced timelines.

Altering an enzyme's specificity or regioselectivity is usually determined by active site residues, while enzyme solubility and stability is often dictated by surface residues. However, in the pursuit of addressing one limitation, you may often affect another. As such, multiple compensatory mutations are required, which can be a long-process with full-gene random mutagenesis approaches.

Proprietary computational workflows are emerging that can be used to accelerate timelines by scanning millions of possibilities to identify the best enzyme for the target reaction. These workflows can traverse natural sequence space (public or metagenomic databases) and predictively find sequences that are as close as possible to an ideal biocatalyst for the transformation. In silico mutations can also be introduced if required.

But enzyme engineering is only one part of the equation. To deliver a robust biocatalyzed process, reaction engineering and enzyme formulation are equally important. For this reason, expertise should be drawn from a range of different specialists. This approach must operate throughout the entire process, starting with enzyme discovery, design and development through to the initial screening, process intensification, and scale-up stages. Especially as delivering the final industrially viable enzyme often relies on identifying the limitations of the biocatalyst in process conditions coupled with targeted enzyme engineering.

It's Time to Calculate the Carbon Footprint of Pharmaceutical Products

BASF has put substantial effort into reducing carbon emissions. A key aspect of our strategy lies in extracting and acting upon the right data – information that allows us to calculate carbon emissions even for individual products.

By Bailey Risteen, Global Sustainability Manager - Pharma Solutions at BASF

Sustainability is a challenge for us all. It often forces us to think differently about how we have always done things. My background lies in chemical engineering and, conventionally, this means scaling processes to very large volumes – but we are now at a time where we need to decouple volume growth with environmental impact. If processes and products are to have a lower environmental impact, we need to approach them from a new angle. For a large chemical company like BASF, which has eleven operating divisions and 700 production sites globally, the task of adopting a sustainability-first mindset can seem daunting. But it is possible.

As a key partner in a number of value chains, including raw materials for the pharmaceutical industry, BASF understands our role and responsibility when it comes to sustainability. In fact, sustainability is a core pillar of our business. BASF has set a goal of net zero CO_2 emissions by 2050, with a 25 percent reduction in CO_2 emissions achieved by 2030 (1). We put substantial effort into embedding sustainability into everything we do, including our business strategy, portfolio steering, R&D projects, manufacturing sites, and more. Discussions around more sustainable ingredients in medicines are on the rise among our customers – and also among patients – and we want to contribute to those discussions in an impactful way.

Sustainability starts with transparent data

To understand emissions tied to a production process – and where there are opportunities for improvement – high-quality data are essential. A few years ago, BASF began working on a digital tool that could pull raw data straight from our production sites (called "primary data") such as electricity demand, waste generation, raw material consumption, and more, and use it to calculate the carbon footprint of individual products (kg CO_2 equivalents per kg product).

BASF has around 45,000 sales products globally and, thanks to the development of this digital tool, we can now calculate the carbon footprint of every single one. The tool does this by using a standardized method (2) that takes into account emissions covered by "scope 1" (direct emissions; for example, from production plants), "scope 2" (indirect emissions from energy purchases), and "scope 3" (indirect value chain emissions; for example, emissions from raw material suppliers). The tool allows us to look at any BASF product, see a summary of its CO_2 contributors, and even view the individual processes where the relevant emissions originate. This tool has been critical to steer our sustainability efforts. The data grant us the opportunity to review our operations, identify opportunities for change, and set priorities.

We can also take these data and contribute to the pharmaceutical value chain by providing transparency to our customers. Showing our customers how we are addressing our hotspots and the carbon footprint of their raw materials may help inform their own sustainability efforts. Today, it's great to see many big pharma, generics, and even CDMO companies setting carbon reduction targets. Dozens of pharma companies have committed to the Science-Based Targets Initiative (SBTi) to align their CO_2 reduction targets with climate science. Even health care systems are taking action – the UK's National Health Service announced its ambition to be the world's first net zero national health service, including emissions from medical devices and medicines (3).

The carbon footprint of ibuprofen

Scope 3 emissions typically make up more than 80 percent of total CO_2 emissions for a typical pharmaceutical company – with around 70 percent of those scope 3 emissions deriving from purchased goods (e.g., raw materials) and services (4).

A key product in our portfolio is ibuprofen, which we produce in Bishop, Texas. Ibuprofen is on the World Health Organization's List of Essential Medicines and several tens of billions of tablets are consumed globally each year. We supply this important API to many companies, so we knew it would be impactful to deep dive into its carbon footprint and conduct industry benchmarking.

Although our digital tool allows us to understand our own product's carbon footprint, industry benchmarking is also important on the road to net zero. For this effort, we worked with Ecovamed – a European consultancy that focuses on life cycle and carbon footprint assessments for the pharmaceutical and speciality chemicals industries. Ecovamed analyzed the different ibuprofen synthesis pathways and manufacturing methods, pulled data from patents and environmental clearance reports, and calculated the carbon footprints of the final ibuprofen ingredient. We gave them primary data from our process and they confirmed that BASF's ibuprofen has the lowest carbon footprint on the market (5).

To date, our ibuprofen has a carbon footprint that is at least 30 percent lower than the industry average. This success can

Why should the pharma industry care about sustainability?

- Healthcare accounts for around 4.4 percent of net global climate emissions (7)
- Pharmaceutical products represent 20–33 percent of health sector emissions (8, 9)
- The pharmaceutical sector emits around 55 percent more scope 1 and 2 emissions than the automotive sector (10)

be partly attributed to the highly efficient production process at our Bishop plant, which uses several Principles of Green Chemistry (prevention of waste, atom economy, minimization of solvents, energy efficiency, reduction of derivatives, and catalysis), won the U.S. Presidential Green Chemistry Challenge (6), and uses 4 steps rather than the 5–7 steps that are more common among other ibuprofen suppliers.

Customers have given us positive feedback about the level of data we provide regarding our products' carbon footprints, and many are interested in how they can incorporate valuable data into their own reporting systems and eco-design principles during product development. Furthermore, in 2021, BASF made the decision to license our digital product carbon footprint platform to software providers. Notably, the software providers have taken the solution to market independent of BASF, ensuring there are no issues with data confidentiality. I look forward to seeing which companies and sectors adopt the digital tool!

This is only the beginning

At BASF, we continue to examine how we can reduce our emissions. Just as scope 3 emissions are a significant part of a typical pharma company's overall carbon footprint, the same is true for BASF; we create some raw materials ourselves and buy others externally. To help address these emissions, we have established a supplier CO_2 management program. In short, we ask suppliers to calculate the carbon footprints of the raw materials that they supply to us and support them through the process.

We all have a role to play in embracing sustainability – no matter where we sit in the value chain. And the key to getting us all aligned? Good data.

Ibuprofen is a large-volume API, and the benefits of reducing its carbon footprint are tangible. The results of our ibuprofen work are exciting, both for drug manufacturers looking to reduce their carbon footprints and for consumers, who are increasingly interested in more sustainable products. We believe BASF's detailed calculation of ibuprofen's carbon footprint represents a case study of what's possible in the pharma industry's pursuit of sustainability. We hope it will demonstrate that these calculations can readily be made, and inspire other companies to think about their own products and operations.

For more information on product carbon footprint, contact BASF at https://pharma.basf.com/general-contact

Footnotes and references

1. *Scope 1 and 2 emissions only; baseline year is 2018.*

2. *ISO 14040:2006 and 14044:2006 for life cycle assessment. Aligned with ISO/TS 14067:2018 for carbon footprint of products and with the Greenhouse Gas Protocol Product Standard [WRI & WBCSD, 2011]. Methodology certified by TÜV Rheinland.*
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NextGen

R&D pipeline
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Future trends

Advanced – But Not Advanced Enough

Great successes are being seen in gene therapy, but there are still gaps in our scientific knowledge – and our manufacturing prowess

By Brian Mullan, Chief Technical Officer at Yposkesi

The gene therapy industry has been building up steam for many years – and it's hard to say if there was a specific turning point that signified the start of the current era of success. Ultimately, I think much of what we've achieved in this field so far comes down to perseverance. When I was working in the field early on, the main discussion points were retroviral vectors and severe combined immunodeficiency (SCID) – sometimes known as "boy in a bubble" syndrome because the normal environment can often be fatal. SCID can be treated with a bone marrow transplant (usually hematopoietic stem cell transplant), but not all patients can be matched with a donor. One famous SCID case is that of David Phillip Vetter, born on September 21, 1971, who spent most of his life in a sterile, protective bubble. No donor match could be found, but as bone marrow transplant science improved, it became possible to use donors who weren't an exact match. David received a transplant from his sister in 1983, but the bone marrow contained trace amounts of Epstein-Barr. The virus evaded pre-transplant screening and David died from a form of lymph cancer on February 22, 1984.

SCID was an early research avenue for gene therapy; however, early gene therapy attempts were somewhat crude and made use of retroviruses – and there were concerns that using a retrovirus to drop in a gene could trigger other diseases, such as cancer. The problems prompted the scientific community to look at the biology of retroviruses and find ways of ensuring that a given gene could be inserted without causing unwanted effects.

For a while, the industry was very interested in adenoviruses as a gene therapy vector, but these were not very successful and caused some safety concerns – most famously with the Jessie Gelsinger case. That said, adenovirus vectors have been very good for vaccines – as we've seen with COVID-19. Adenovirus-based gene therapies have also been approved in China, but other countries have not followed suit.

Eventually, there was a jump to the adeno-associated virus (AAV) as a vector. It was considered a niche area at first but people kept digging away at the science – and eventually it led to approvals for Luxturna and Zolgensma. The approvals

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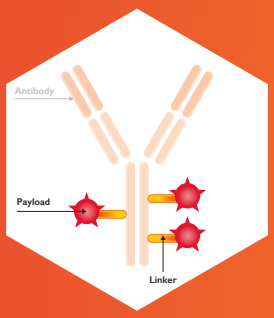

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of these therapies were significant milestones for the gene therapy industry and have catalysed growth in the field. Yes, there are still great challenges that the gene therapy field faces – costs are high and these therapies can come with significant risks to patients. However, I can't see us going backwards!

Empty or full?

There are several areas where gene therapies can be improved. AAV is the most common vector used today for in vivo gene therapy, but around 50 percent of the population have pre-existing immunity to AAV, which means they are unlikely to benefit from the therapy. If we can screen these people, they can be excluded from trials or alternatively we could look at ways of increasing the dosing.

Another key area of focus for AAV vectors is the ratio of empty capsids to full, and whether this affects toxicity and immunogenicity. In September 2021, the FDA held a meeting about dose and toxicities – with capsids being a key discussion point. Full capsids are required for therapeutic efficacy, but it's not known if empty capsids are a problem. However, because they do not contribute to efficacy (although some researchers believe there could be some benefits to empty capsids) there is a logical argument that we should reduce them.

A virus' natural replication system is very efficient, so using a wild type adenovirus to help produce an AAV would result in lots of full AAV capsids. However, once scientists begin to engineer the virus – which is often required for drug development – the replication efficiency reduces and the yield of full capsids decreases. Science and understanding in this area will continue to evolve, but we do know that mixing elements from different serotypes or tampering with the biology has a negative impact. In short, the more natural the things are, the better the yields appear to be.

Many scientists – and companies – are working to find solutions to this capsid issue. But the concern here is that whoever finds a good answer is more likely to patent it than share the information – after all, that is the nature of the pharmaceutical industry!

A wish list of new technology

There are many other challenges that we must address in gene therapy. In some ways, we can apply lessons learned from mAbs because the process of making mAbs and viral vectors is quite similar. A key technology for viral vectors is likely to be single use equipment – and the mAb area can teach us a great deal about these systems. Fixed stainless steel for vectors may come, but there are too many variables in the gene market right now for companies to consider such a rigid manufacturing infrastructure, so single use will likely be the way forward for the immediate future.

However, we can't take all of our knowledge from mAbs. Viral vectors are made using plasmid transfection, which can have scale limitations. Using a 1000 L or 2000 L bioreactor for viral vectors will improve throughput and costs, but the volumes of plasmid and transfection reagents, as well as mixing at large scale, are significant challenges (e.g. cost, process reproducibility). New technology in this area will definitely be helpful. In addition, we could also benefit from improvements in the price of plasmids – they are very expensive for what they are, especially for GMP grades!

Cell lines for gene therapy also face issues. With mAbs, you can generate a cell line within a couple of months; but this isn't possible when it comes to cell lines for a gene therapy vector. Making cell lines for gene therapy vectors is a huge effort because we're using 30-year old technology that controls gene expression – the cells do not like it when you constitutively express certain viral genes, even at a low level. Right now, most companies are using the transient transfection route because it's flexible and you don't need to invest in a cell line for a product that may not eventually proceed to market. However,

What's so special about gene therapies?

Why are gene therapies so fascinating? For me, it comes down to the nature of the correction and the specificity that gene therapies allow. If we look at classical chemical medicines such as kinase inhibitors, drug developers do the best possible job they can to modulate a biochemical effect, but there are always off-target effects. Biologics ramp up the specificity, but you're still at the mercy of the biology, and sometimes when you catch your target, it doesn't do what you want it to. Gene therapies provide even greater specificity, allowing drug developers to correct problems at the genetic level, rather than on a chemical or biochemical level.

Gene therapy is also highly complementary to other medicines. With any disease, patients often start out with a generic type of medicine. If that doesn't work, they move to a stronger medicine. In some cases, antibody medicines are available. Now gene therapies are being added to the mix. It is important for patients to have options – and gene therapy is a very good option.

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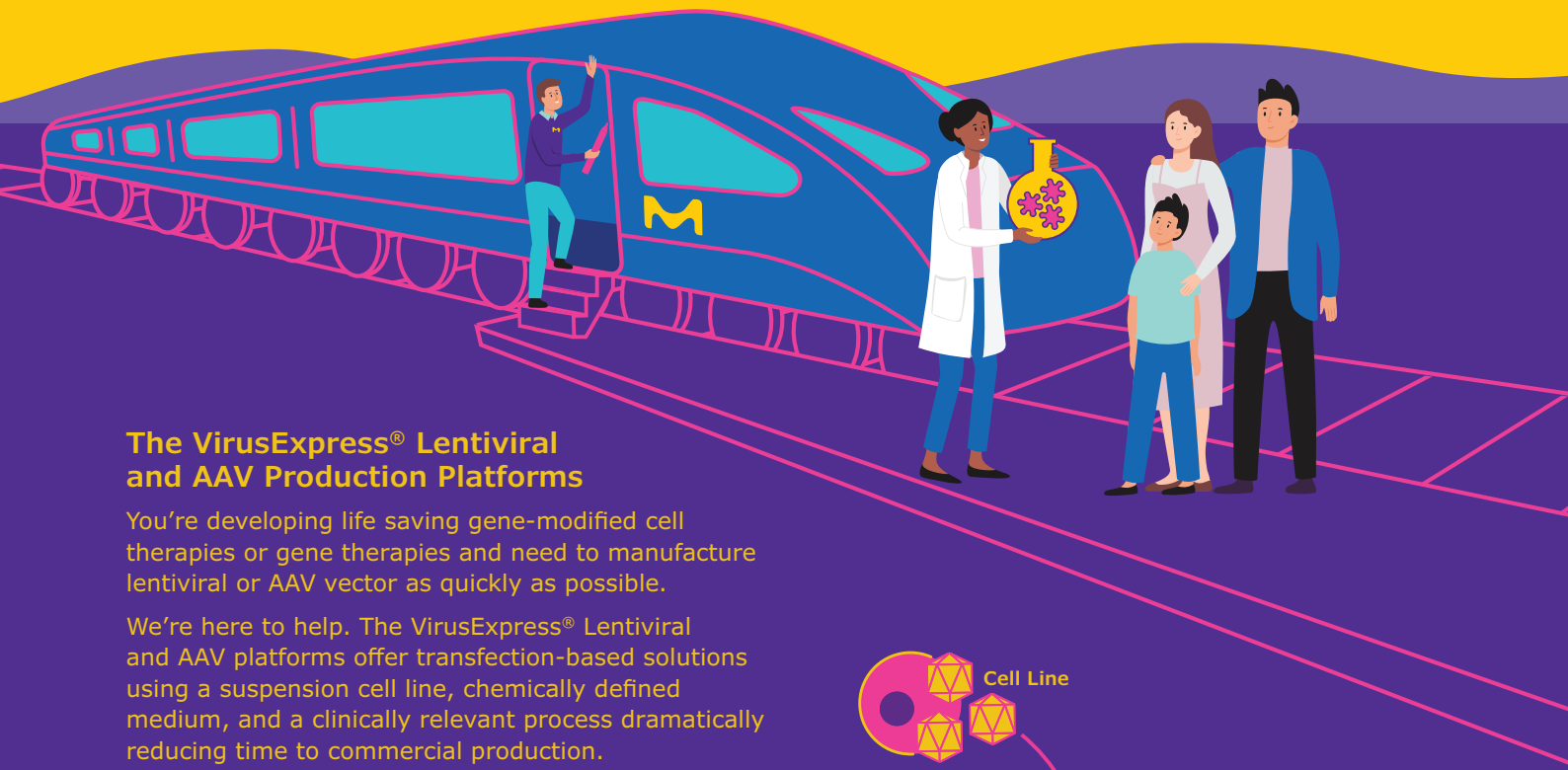

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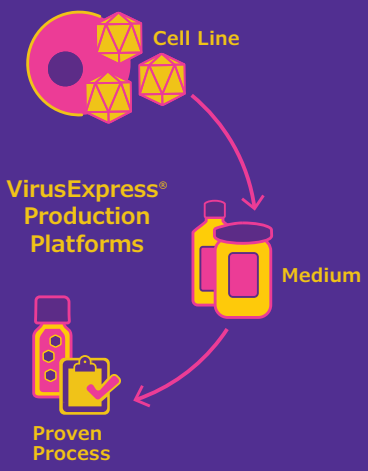

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Gene therapy safety

In August 2022, reports emerged that two children had died of acute liver failure after receiving Zolgensma. Gene therapies can transform patient lives, but they do come with risks. Zolgensma is not the only therapy that has faced such issues; other companies have faced clinical holds on trials because of questions around safety. If the sponsor cannot explain what has happened and why, the FDA will put a hold on the trial while the matter is investigated. Unfortunately, these investigations can also affect other therapies in the same category.

There has been a lot of stop–start in gene therapy research, with knowledge improving in a reactive way. Clearly, companies do not advance therapies into clinics with the expectation that some patients will suffer serious effects. But correcting part of a genome does not come risk free. So the big questions are: What is the risk? What are the benefits? And what is the balance? As new science becomes available we can better answer these questions – but a lack of understanding and a reactive approach seems destined to carry some risks. Put simply, we need more research and more clinical experience.

transient transfection can be limited in terms of cost, yields, and scalability. We need new approaches and technologies that can more quickly generate cell lines for viral vectors.

Purification represents another opportunity for progress. With antibodies, you are somewhat spoilt for choice when it comes to purification, with a large range of chromatography resins and filters available. And there is a lot of expertise to go around. But for the purification of viral vectors, the technology offering right now is limited. Fortunately, progress is being made; for example, Thermo Fisher Scientific, Cytiva, and Repligen are all active in this space, though there is often a reliance on users to help bring new technologies to market, which can be frustrating for users. I'd like to see more companies putting out solutions that are truly ready for use.

Finally, I would like to see more work in the area of analytics. Right now, we don't understand the products very well or what methods we need. I like to use the analogy of nailing jelly to the wall! It seems as soon as you have qualified and verified the right analytical method, people start questioning whether it is actually the right method, or a "better" method comes along. Each method also seems to have its pros and cons; for example, analytical band centrifugation does a good job of determining your empty:full capsid ratio, but you need a lot of material and you can only perform the analysis at the end of the process.

If you want to follow your empty:full ratio throughout the process then there are very few methods available. You can use cryo-electron microscopy, but this is expensive, very specialized, and the results take weeks. There is also capillary ion exchange chromatography, which can potentially separate empty capsids from full capsids, but it can't do partials. The equipment is also expensive and if the assay gets registered in a filing – and then the technology moves on – you are stuck with the equipment.

Are empty:full capsids going to be important a few years from now? We don't know – so investment decisions are being made based on incomplete information, with the industry chasing its tail to catch up to the next thing that comes along in analytics. I'm pleased to say there is at least a lot of transparency in this area; many different companies are pushing different technologies, which is leading to a lot of discussion. Ultimately, this activity should help decrease costs and lead to more options coming onto the market.

Right now, the testing landscape can be confusing, seeing companies left with questions about what technology is right for them and whether they should wait another year to see if anything changes.

In it together

How do we move forward? I would like to see the industry working more collectively to advance the gene therapy field – product developers, CDMOs, equipment companies, and regulators. The mAbs field has been growing since the 1990s – with huge strides made in the 2000s. Gene therapy has a way to go, but we can get there. One significant call to action is knowledge sharing. Right now, this is not where it should be. The industry goes into research holes to solve issues and then somebody pops up with a solution, but the discussion on what has been learned and what it means is not as transparent as it should be. It can be hard to know what's going on and who's working on what, which leads to many people working in parallel on the same problems and making the same mistakes – a real waste of resources.

It's understandable that companies want to maintain a competitive edge, but the lack of sharing and transparency is not helping the industry as a whole. Slowly, we will see change – especially as more partnerships are formed between developers and their CDMOs and equipment companies, and also via industry forums such as BioPhorum and ARM. It would be naive to think we won't hit more bumps along the way, but we'll be able to get over them faster and easier as a collective.

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Business

Economic drivers
Emerging trends
Business strategies

The pharma industry is steaming ahead with the development of new medicines and technologies, but is it attracting the talent it needs to continue its current success? Industry experts share their tips on how companies can improve their hiring tactics…

Do you think young people are aware of the career options available to them in pharma?

Singhal: It would be hard to miss that pharma is one of today's fastest-growing industries, but we can do more to inform young people about the opportunities that exist for those with math and computer science degrees. Pharma is heavily reliant on state-of-the-art technology and medicine; many young graduates with backgrounds in life sciences, chemistry, mathematics, operational research, and other disciplines can find fulfilling careers in the industry. Pharma offers a plethora of career paths, including research, sales, manufacturing, quality, and data analytics (which is particularly hot right now). And no matter which pharma career path a new grad chooses, knowing they are in the business of improving patient lives should be hugely satisfying!

Jacoby: It has always been difficult to showcase the roles available in the pharma industry. There are a wide range of drug types and areas of focus – from supply chains to IT to development to clinical – and different skillsets are needed for each. Because of the variety and complexities of these roles, there is a lack of awareness of just how many options there really are in the industry and what type of background is necessary for each.

Bowen: I think there is awareness, but mostly among those seeking roles as scientists or engineers. Very few are aware of the various innovation-focused roles in the life sciences or the technologies used in the industry, unless it has formed a part of their degree or studies.

Clockwise: Laura Jacoby, Application Specialist at Apprentice.io; Shikha Singhal, Principal and Leader of People Practices at Axtria; Keith Bowen, Laboratory and Manufacturing Execution Systems at Apprentice.io

How are pharma companies promoting open positions?

Jacoby: There are different websites on which companies advertise positions. Most pharmaceutical organizations also have dedicated career pages on their websites with job listings, as well as a presence on LinkedIn and other social media outlets. Attending career fairs at universities and providing internship opportunities are also good ways for pharma companies to promote careers.

Singhal: Companies should consider partnering with colleges and participating in activities such as guest lectures, career fairs, and webinars to teach young graduates about the lucrative career paths in pharma. It's also possible to partner with industry associations, such as the Pharmaceutical Management Science Association (PMSA), a not-for-profit organization whose mission is to raise awareness of and promote the use of management science in the pharma industry. At Axtria, we also

conduct periodic educational seminars, training programs, and the occasional hack-a-thon to target young professionals who possess specific skills and excite them with cool problems to solve!

Do pharma companies have any concerns about recruiting and retaining young talent?

Jacoby: Yes, but I don't know how seriously they take them because there are no unions in pharmaceutical companies. I have seen a change in the industry's push to cut costs with greater outsourcing, fewer employee perks, and less access to pensions and other attractive benefits. All of that is unfortunate, because most candidates are passionate about working in the field. I'd like to see the industry reward hardworking candidates more.

Singhal: For us, the biggest concern with recruiting young or relatively inexperienced talent is finding ways to make individuals productive early in their careers. For them to be effective, young talent must have the required technical, functional, and soft skills, as well as a solid understanding of the pharma domain. This calls for significant investment in their learning and development. Not many organizations have a learning and development process that can really handle the scope of this task.

Another challenge of retaining talent is that employees become more valuable in the market as they acquire these skills. Organizations must invest in robust talent management and retention strategies to ensure that their employees have a clear career path, continuous growth and learning opportunities, ample recognition, and meaningful work.

Bowen: With the biotech sector's rapid growth, it is difficult to hire and retain staff – and has been for some time. As new, more flexible technologies become available to the life science industry and pharma shifts toward new manufacturing methods, it's a great time for new hires to enter the field.

What is today's workforce looking for in an employer?

Bowen: The labor market is short on resources and today's applicants have high expectations. Companies need to meet them to attract and retain talent. Today's workforce is looking for modern, flexible ways of working. The old ways of doing things do not appeal to younger workers. They want modern technology that feels comfortable and familiar as they work within a lab or suite environment. In addition, access to enhanced training materials and guided workflows that allow them to work with confidence is key to ensuring success. They're also looking to their employers to help them establish a career path.

Singhal: The pandemic has significantly changed the way people look at life. The workforce is looking for greater flexibility to integrate their work and personal lives. Consequently (as Keith points out), employers must change their expectations.

Wellness has also assumed a new dimension, with increased emphasis on socio-emotional and mental wellbeing. Employees now expect their employers to play a more significant role in their holistic wellness. As they search for more meaning in their lives, employees are looking for jobs that help them achieve a larger purpose, allowing them to contribute to the betterment of society.

What tips would you give to hiring managers who are looking to recruit young talent?

Bowen: Social media is the number one way young people communicate today. Companies should engage with platforms such as YouTube and Twitter to respond to the day-to-day questions potential recruits may have about roles!

Companies can also get involved with universities and students prior to graduating, so that they understand the potential opportunities out there.

Singhal: I would emphasize that it is essential to strike the right balance between coaching and managing. As a coach, you should help young talent uncover their strengths, motivations, and priorities, leading them to discover the right career path. As a manager, you should encourage young recruits to see how the big picture relates to both their life and the organization's purpose.

A Good Culture Keeps Good People

Investing in a robust, fulfilling company culture is the best way to thrive in the current challenging recruitment landscape and to achieve long-term success as the biotech industry inevitably rebounds

By Jonathan Thon, Founder and CEO of STRM.BIO

It's not enough for a biotech company to have great technology, an experienced management team, and deep pockets. If that were true, our sector wouldn't have an 85–95 percent failure rate. In this challenging and hyper-competitive industry – and especially at a time when the industry is reeling from a major market downturn – the only true differentiator is innovation: finding creative solutions to important problems by betting against the current consensus and being right. And to do that, you need the right people.

Consistent innovation is a product of teamwork and a supportive environment. Good teams can be directed to difficult projects and produce successful outcomes, but promising projects will die in the hands of poor teams. It's also not enough that companies hire on performance; they must also establish a supportive, collaborative culture in which a team can perform, adapt, and innovate as technology and ideas evolve.

Keep your people

The recent market spike through 2020, fueled by investor interest in innovation related to the COVID-19 pandemic, created fierce competition for technical and executive talent and led to rampant salary and title inflation. Despite the most recent market downturn, a lot of that capital is still in the system. Talented employees with depreciating stock options that were assigned during the market's peak may be tempted to jump ship to a high-priority program that has already passed a belt-tightening review at another company.

Right now, companies cannot afford to lose their best employees, so a conscious focus on culture is an important investment. Although it's important to pay competitive salaries, there will always be another company that can afford to pay more, so any candidate recruited solely on compensation is just as likely to leave based on compensation. Culture, by contrast, is unique to each company. A culture that empowers employees and supports their development will have value beyond money for many innovative, growth-minded individuals. Culture doesn't just help retain great employees; it allows companies to get the most out of their people and fosters the motivation that drives creative thinking and problem-solving.

When deciding whom to interview at STRM.BIO we set a very high bar for technical skill, but the final hire is always based on cultural fit. We seek talented individuals who can nucleate strong teams around critical problems. This approach to recruitment requires more time and consumes more bandwidth, but I think it also promotes retention by ensuring that employees and the company culture are matched.

We are not alone in putting culture at the center of our approach to recruitment and retention practices. Recently, the Chief HR Officer for AVROBIO, Georgette Verdin, discussed their process of investing additional time in employee development to continually "re-recruit" their talent – applying the tools and strategies of external recruiting to your top employees to keep them engaged and motivated (1)

ImmunoGen's SVP and Head of HR, Audrey Bergan, emphasized the importance of trust and transparency in achieving their high retention rate, saying, "There will be times you ask your employees to believe in you, and they won't follow you if you pretend to have all the answers (2)."

Achieving trust and transparency is easier said than done. It requires accountability and clear communication across the entire company, and how these values are implemented and enforced is a product of the culture a company invests in developing. For example, it can help to give employees the right to understand and challenge the rationale for organizational decisions. At my company, we hold monthly all-staff meetings in which updates are provided and senior staff held accountable. Everyone is encouraged to speak and we deal directly with "elephant in the room" topics. This can be jarring, but it forces a level of transparency and communication that keeps the team aligned and focused on what matters most.

During difficult times, it can feel tempting to focus on finding ways to cut costs and to push harder and faster on technical milestones. But difficult times don't last forever; in fact, the signs are good that the industry will rebound soon (3). When the market recovers, the current talent scarcity and retention problems will only get worse as companies accelerate hiring tactics. My experience tells me that the best talent will be looking for fulfilling, purposeful work in a culture that supports their personal growth. A failure to invest in this crucial aspect of leadership while navigating the current challenging landscape could leave many companies with a significant talent gap on the other side.

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Pharma and Fordism

Sitting Down With…
Gen Li, CEO, Phesi

What formative events defined the early days of your career?

When I started my career at Bristol Myers Squibb, I was in charge of operations in various "other" regions. One such region was South America, which had been neglected as a region for clinical trials because it had a reputation for running everything too slowly.

I deployed a pretty simple concept from operations management, called "critical path analysis." Upon analysis, one problem became salient: the drug supply was often lagging months behind. Why? Because South America is the backdoor of the US, it has always suffered from illegal drug trafficking. Experimental medical drugs could end up contaminated with illegal drugs, which – understandably – demanded more scrutiny and was slowing the whole process down.

We got pharma companies directly involved in helping improve matters and you can see the results today: South America is becoming an increasingly important place for clinical development. I walked away having learned an important lesson. Despite the pharmaceutical industry employing some of the brightest minds in the world, fundamental problems remain unsolved! And I am up for the challenge!

Why did you start your own company?

I set up Phesi for two reasons. The first is simple: I needed to support my family. The second is more glorious: I wanted to solve the major problem in clinical development – cost.

The industry is astoundingly primitive in how it plans and conducts clinical trials. A comparison with the history of the Ford Model T sheds some light on the problem. Henry Ford had the idea that every family should own a car. At the time, that was unimaginable. However, he had a theory to back up his idea called "scientific management." It was formulated by the mechanical engineer Frederick Winslow Taylor and applied with great effect by Ford in his assembly line manufacturing business.

The approach had such a great impact on history that we now call it "Fordism." Put simply, my dream is to bring a kind of "Fordism" to clinical development. At Phesi, we're not here to patch and repair the field; we're here to build a conceptual framework.

You say you're an academic at heart – how did you get into business?

University was extremely important to me because I was in the first generation of students to attend China's universities when they reopened after around a decade of closure during the Cultural Revolution. Mao Zedong had died, and society was entering a new era. I chose to pursue organic chemistry because I had long felt it was the most practical.

When my studies took me to the US, I managed to quickly overcome my culture shock and get a paper published in Science. Interestingly, the substance (agmatine) we discovered is now part of the mechanism for various new drug developments. It was a huge honor because it's something many researchers will never achieve in their lifetime. However, at this time I was also thinking hard about myself, and whether I was best suited for academia. Eventually I decided that, given the nature of my personality, benchwork was not my future. I decided to go to business school, and there I got my MBA and completed my transformation.

What changes have you seen in the role of data in pharma over the years?

Not so many years ago, data in pharma was good for little more than producing pleasing animations – as with many other fields. So if we compare the early days with today, we can see that data is getting better and better at describing real human beings and real actions. The pharmaceutical industry is riding the revolution in our capabilities to run calculations and store information.

That said, I would also advise caution regarding expansive claims about data science. Pharma has seen similar surges in hype. From promises regarding high throughput screening to "Opportunity Seeking Blockbuster" strategies, none of these hype trains ended up going anywhere. Right now, I can see that some pretty chaotic ideas are being sold – and they will damage the playing field. We all need to make sure that we can deliver on our promises.

Tell us how your attention has recently turned to Ukraine…

As individuals, we have career responsibilities and we have social responsibilities. As a company, Phesi has commercial responsibilities and social responsibilities too. To me, these are the same. Paying attention to serious issues and finding opportunities to shed light on them is one way to attend to one's social responsibilities. When COVID-19 hit, we reported extensively on how it was impacting clinical trials, and our reporting on the effects of the war in Ukraine is essentially a continuation of this effort to shed light and help people.

At the affected investigative sites, many people's livelihoods are at stake. Many of these sites are very small businesses with very limited financial capabilities. If we don't pay attention to their struggle, they will die out and the wider ecosystem will be hurt. Ukraine was an important country for clinical trials in breast cancer, so harm to that ecosystem will have a longer-term knock-on impact. For all these reasons, we want to help by raising awareness and spreading the word.

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