the Medicine Maker

SPECIAL SERIES:

Technology

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EDITORIAL

Lights, Camera, Action…

Who's writing the 2023 technology script…?

It has been fascinating to collate technology-centric articles for this special eBook, and to discover the technology and innovation behind drugs that help transform, extend, and save the lives of patients everywhere. By looking a bit closer at every manufacturing industry, where the end product is often the star of the show, you will find the unsung heroes that help to make that star shine. In every case, these heroes are the technology and the people that innovate and make that technology faster, cleaner, more efficient, and more reliable. Respectively, they are the beating heart and the brain cells that toil ceaselessly behind the scenes to bring production to life.

In this eBook, we point the spotlight at technology innovation. First up is our 2022 Innovation Awards showcase, featuring bispecific antibody manufacturing methods, gene synthesis accelerators, chromatography columns, and more. A tough act to follow, I agree, so we also got in touch with the companies behind the top three technologies featured in our 2021 Innovation Awards. Also included – a selection of articles on innovation and disruptive technologies.

The scene is set; let's all go to the lobby. Clip your tickets, take a seat, and enjoy the show. Pass the popcorn.

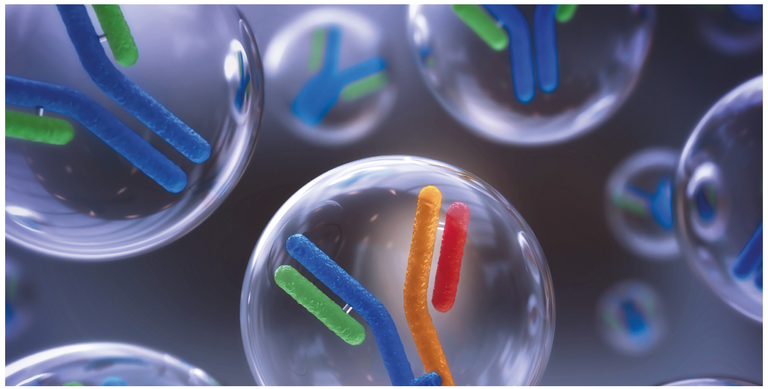
By Rob Coker, Deputy Editor of The Medicine Maker

THE INNOVATIONS AWARDS 2022

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

Towards the end of 2022, The Medicine Maker announced a shortlist of the year's most innovative new technologies in drug development and manufacturing - as nominated by the community.

Apisolex Polymer
Injectable-grade, polyamino acid-based, solubility-enhancing excipient
Produced by Lubrizol Life Science Health



BioXp 9600
Synthetic biology workstation for accelerating synthesis of genes, clones, and variant libraries *Produced by Telesis Bio*

bYlok Technology
Solving the light-heavy chain mispairing challenge in bispecific antibody manufacturing *Produced by Lonza*

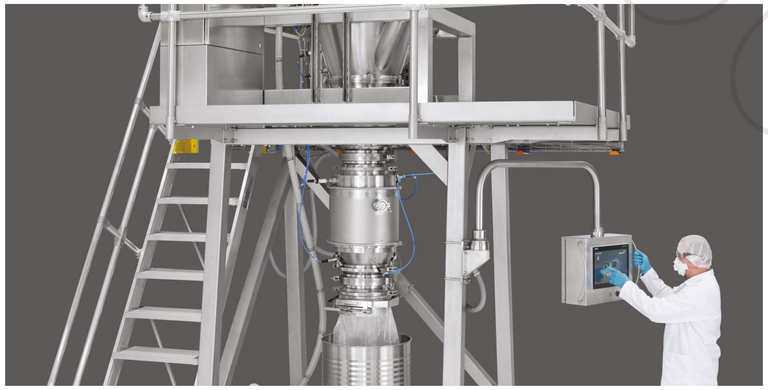
Foresight Pro Chromatography Columns, CHT Ceramic Hydroxyapatite
Prepacked columns to support biomolecule purification
Produced by Bio-Rad Laboratories, Inc.

Gibco CTS Xenon Electroporation System (Xenon System)
A customizable, scalable electroporation system for GMP-compliant cell therapy manufacturing *Produced by Thermo Fisher Scientific*

Korus
Cleaner cell populations through elutriation *Produced by Invetech*

More...

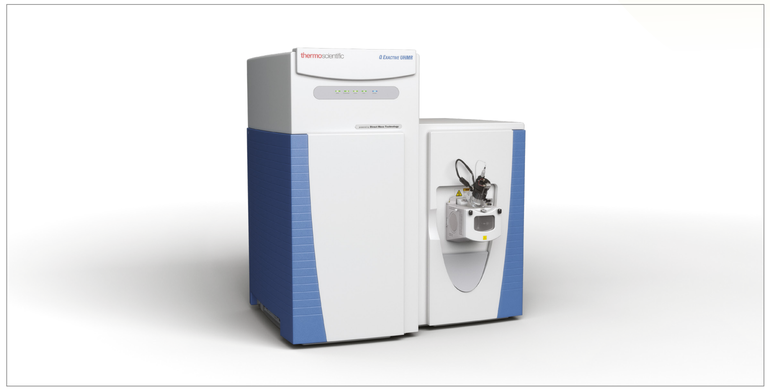
Pin Mill PMV-320
Milling/micronizing platform that renders product ignition or explosion impossible *Produced by Frewitt Engineering Works*



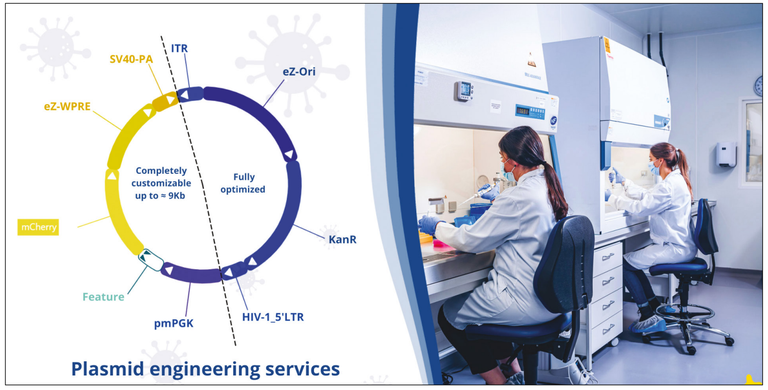
Quantum Flex Cell Expansion System
An automated and functionally closed cell expansion system
Produced by Terumo Blood and Cell Technologies

SkillPak BIO and Octave BIO
A bench-scale multi-column chromatography system with bespoke columns *Produced by Tosoh Bioscience*

Thermo Scientific Direct Mass Technology Mode
Simultaneous charge detection for analysis of previously unmeasurable analytes *Produced by Thermo Fisher Scientific*



Transgene Plasmid Engineering Services
An engineering service for custom viral vector manufacturing
Produced by Polyplus



Zeno SWATH DIA
Significant sensitivity gains to MS/MS data acquisition
Produced by SCIEX

VOTING

Voting to decide the grand winner will be underway until March 16, 2023. *Vote here*

Can high cell density cryopreservation simplify processes?

Judge for yourself.

SigmaAldrich.com/HCDC

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UPFRONT

Finding the True Meaning of Disruption

When it comes to innovation, companies often describe their work as disruptive. But how many of the innovations making their way onto the drug development and manufacturing scene truly have the capacity to change the industry for the better?

Disruptive is a term that is overused in the life science industry. It's often applied to marginal technological upgrades or even adapting a tried and true technology to a new application. That said, the current transformation in our industry is both exciting and unknown – and, by definition, disruptive.

Much like the scientific revolution currently being fueled by novel modalities, such as RNA, cell therapy and gene therapy, we are also seeing swift technological advancements. Pharma 4.0 is a complex ecosystem of tools, systems, and technologies that will amplify the industry's capabilities to a degree nearing science fiction. The age of lights-out, cloud-based, fully automated, and self-learning facilities is entering the biopharma industry, and progressing at a rapid pace.

As an industry, we must prepare for the profound changes the next two decades will bring in the form of curative therapies being manufactured in factories and processes that will have little resemblance to the ones we know today. Automation will help us get there. But it is our responsibility to harness the power of this revolution to make cures and therapies accessible to patients around the globe.

By Noel Maestre, Vice President, Life Sciences at CRB

IN MY VIEW

There's Nothing Artificial About AI's Potential in Pharma Research

Can AI realistically transform data management in pharma? Yes. And it's already begun.

Change in clinical research is inevitable – so it's essential that we, as an industry, understand the impact of these fluctuating variables on patient outcomes. But when there are hundreds, if not thousands, of patient records to trawl through, how can companies accurately predict the influence of trials on patient lives? Traditionally, that's when the task truly becomes difficult. But advances in data science, machine learning (ML), and AI enable companies to mine billions of data points – and it's starting to make the task much more manageable.

Until recently, documenting pharma research was a painstaking, mostly manual process of cross-referencing public repositories of pharmaceutical data, information in scientific and medical journals, and the company's intellectual property from its own drug development and testing experience. All of these data are available digitally, which makes any "manual" methods associated with collection and analysis increasingly problematic – and that limits the value of data relative to the resources required to manage it.

Processing these enormous tranches of data to support drug development strategy and better patient outcomes is the central challenge facing many drug developers. Fortunately, advances in data management and analytics are providing pharma developers with a more practical and simplified means to collect, collate, categorize and cross-reference trial and patient data, and then mine it for actionable insights, as well as business and patient value.

In my view, AI can deliver immense value to companies looking to upgrade their data management processes. We can see this by taking a look at real-life applications of the technology. For example, we recently collaborated with an international pharmaceutical research company that wanted to improve its process of reviewing critical information on drug performance and patient outcomes. To support the development of their lead candidate, researchers and program leaders needed a method to quickly and accurately process the massive amounts of data emerging from their own trials, as well as the data from public/private sources and the R&D firm's own cancer cell line encyclopedia.

Using a select set of data science tools and techniques, we built an automated solution that ultimately helped them identify optimal doses of drugs dramatically faster. The solution adopts text mining to automatically review more than 10,000 online resources, including medical journals and scientific research publications. Applying an agile development model, the collaborative AI team designed and built an automated data-driven pipeline that intakes the vast range of disparate data, normalizes it, performs analytical processing, and delivers easily understood reports on outcomes.

Through data science and advanced ML and AI-supported analytics, the automated pipeline solution helped the researchers move away from their cost and labor-intensive manual process for cross-referencing research from clinical trials on cancer drugs.

But that's only one example of how AI can be useful for data management in the clinical trials arena. In the future, we should expect to see better recommendations on dosages, cross-indexed to a broad range of relevant and actionable patient information that can be used by relevant pharma stakeholders, including physicians.

We're now at the point where we are laying the groundwork for accelerated, more pertinent R&D processes. If we continue to explore the capabilities of AI and ML, we will ultimately be able to create improved treatments for patients across a spectrum of diseases.

By Avi Kulkarni, SVP Life Sciences SBU at Cognizant Bio

INTERVIEW

Keep Connected

The winner of the 2022 Innovation Awards is still being decided. In the meantime, let's look back on the winner of the 2021 Innovation Awards - Nuvolo. Here, we find out what makes their software so special.

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

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

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

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

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

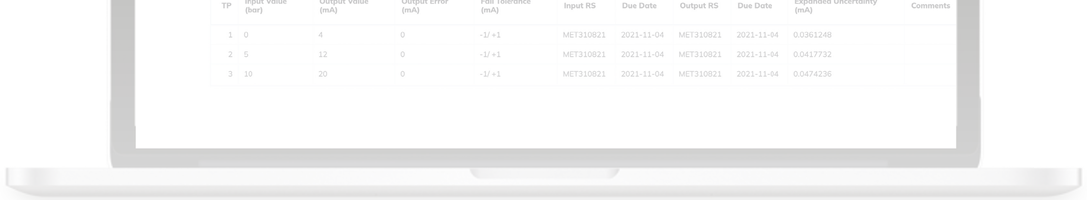
So overall, the strategy and direction of the company did not change because of the pandemic, but we did see new priorities emerge.

What does Connected Workplace do?

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

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

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



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

How does your solution apply to life sciences?

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

Where does calibration come in? Why is it important?

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

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

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

Are there any other benefits to using your software?

Calibration needs to be an integral part of comprehensive asset management. Historically, calibration documentation has been provided by external service vendors without any actual data. Connected Workplace for Life Sciences provides much more than just a certificate indicating that a device is calibrated properly. There is a wealth of calibration data that can be integrated with other maintenance data, which enables companies to make data-driven decisions based on asset health, historical trends, and service and replacements costs. Are assets being calibrated too often? Or not often enough? These questions can be difficult to answer with traditional paper-based systems but easier to analyze when there is a large, easily accessible dataset.

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

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

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

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

What sets a good interface apart?

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

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

READ THE FULL ARTICLE ONLINE

INTERVIEW

The Cutting Edge of Biopharma Analytics

How can new analytical tech help biopharma manufacturers? We speak with one of our 2021 Innovation Award runners up.

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

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

What makes your work exciting?

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

In a nutshell, what does the Waters system do?

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

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

How were you involved in the development of the system?

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

What's the origin story of the system?

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

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

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

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

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

What specific challenges can the system solve?

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

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

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

What are the main challenges faced when developing analytical systems?

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

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

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

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

However, there are good reasons for laboratories to pursue upgrades. If new technologies can improve analytical throughput effectively, or measure multiple critical quality attributes of a drug product from a single LC-MS assay, or measure the product attributes of new modality therapeutics during development, then the long-term benefits of upgrading to the newest, state-of-the art analytical technologies will easily outweigh the initial burden of installation and training.

How will analytical technology continue to evolve?

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

INTERVIEW

It's All About Connecting

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

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

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

Why are good connectors key for the biopharma industry?

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

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

terms of performance and reliability concerns. From a supply chain perspective, a good connector should bring customers peace of mind, as it helps customers create pre-engineered systems, which makes for a repeatable and predictable process.

What makes the Micro CNX connectors stand out?

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

What inspired the launch of these connectors?

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

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

Overall, they were looking for a simpler, faster, and smarter way to make sterile connections in their processes.

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

Tube welding, especially in smaller format tubing, is deeply ingrained in our customers' existing processes. It's an approach that has been used to enable closed processing for decades, but it comes with potential drawbacks and risks that can compromise sterility. A large part of our task is to teach people that an alternative exists. Connectors like ours offer a more reliable, consistent means of connection, and we want customers to know that. Connectors are still a relatively new technology, especially in the field of cell and gene therapy, so we know that it's important to keep sharing our knowledge with customers and demonstrating how effective connectors can be in small-volume closed aseptic processes.

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

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

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

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

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

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

Single-use aseptic micro-connectors – such as CPC's MicroCNX connectors – are designed to connect in a sterile manner with small-bore tubing. This is something completely novel to the industry.

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

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

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

SPONSORED CONTENT

Streamline Your Seed Train By Using High Cell Density Cryopreservation

Looking to increase your biomass and significantly accelerate your cell expansion processes? Simplify your seed train intensification with HCDC!

The seed train is a critical part of the bioprocess, generating sufficient biomass to inoculate the production bioreactor and begin protein production in an optimized manner. In a traditional seed train, this is achieved by passaging cells from a working cell bank vial through increasingly larger cultivation systems including shake flasks, rocking motion bioreactors, and stirred tank bioreactors.

With seed train intensification, the goals are to lower manufacturing costs, achieve higher process throughput, increase flexibility, and reduce risk. This can be achieved by implementing perfusion operations in cell bank manufacturing to accelerate expansion and achieve greater cell density in the N-1 bioreactor and/or using high cell density cryopreservation methods, on which we will focus here.

The traditional process of thawing a single vial of cells to initiate cell expansion for a commercial manufacturing batch is time-consuming and requires open cell culture operations, increasing the risk of contamination. Use of cells banked at high density and high volume, which can be fed into the first seed train bioreactor, can streamline the overall process.

To reduce the duration of cell expansion, higher density cell banking approaches in larger vials (5 mL) have been used. This approach results in some improvements but does not eliminate the contamination risk due to manual transfer of cells. The shortcomings of this approach are overcome with use of high-cell density cryopreservation (HCDC) single-use assemblies, in which single-use bags containing larger volumes (100-250 mL) of high cell density cell banks (50-150 x106 cells/mL) are produced using a perfusion process.

Traditional seed train expansion can require up to 20–30 days before inoculation of the production bioreactor. In contrast, incorporation of HCDC into the process enables a significant reduction in the time required to inoculate the production bioreactor.

In addition to time savings, specially designed cryobags eliminate open cell culture operation steps, lead to better reproducibility in seed train expansion, and decouple cell expansion and batch production. Unlike vials requiring expansion during each campaign at the production site, cryobags can be distributed globally from a central expansion facility to global production facilities, improving the consistency of the inoculum of the production bioreactor.

JUDGE FOR YOURSELF!

INTERVIEW

Sounding Out Effective Cancer Treatments

Oxford University spinout OxSonics has developed a unique use for ultrasound technology to make anticancer treatment more effective.

OxSonics Therapeutics was spun out of the University of Oxford's Institute of Biomedical Engineering in 2013. Its proprietary technology platform, SonoTran, combines innovative particles co-administered independently with an anticancer drug. CEO Jérôme Marzinski tells us how this technology can benefit the anticancer research community.

What is SonoTran and what can it do?

The SonoTran particles carry a pre-formed, stabilized air bubble that creates sustained levels of "inertial cavitation" (bubble expansion and collapse) when exposed to ultrasound at the tumor site. The SonoTran System, an ultrasound device, "activates" the particles, creating an inertial cavitation effect that produces localized pumping to enhance anticancer drugs' penetration into and throughout tumors, thereby improving efficacy and reducing toxicity.

SonoTran is drug-agnostic and requires no drug reformulation, enabling its use with both existing and novel therapies. Treatment can be imaged and monitored in real time using proprietary mapping technology overlaid onto medical images to allow healthcare professionals to see as they treat.

What stage of development are you at?

SonoTran is currently in a phase I/IIa clinical trial in patients with liver metastases from colorectal cancer. We are combining the technology with standard-of-care anticancer therapy, which includes cetuximab. This first-in-human clinical trial started in January 2022 after nine years of work to get the technology to this point. Data from the initial safety cohort show that, as anticipated, SonoTran is well tolerated.

What led you to focus on solid tumors?

There is a need for new technologies to address the performance limitations of current anticancer drugs, which are restricted in their ability to penetrate solid tumors – particularly in the case of targeted biologics such as mAbs, ADCs, and oncolytic viruses.

Several factors combine to make solid tumors a challenging environment for anticancer biologics delivery. The tumor vasculature is tortuous, highly heterogeneous, and leaky, with endothelial gaps in the range of 200–1,200 nm (many times larger than the 5 nm gaps typical of healthy vasculature). This causes increased interstitial fluid pressure through unregulated extravasation of fluid. In colorectal liver cancer metastases, fluid pressures are reported to be 10 times higher on average than in normal tissue (21 mmHg versus 2 mmHg). Although the peak distance between a cell and the nearest blood vessel in healthy tissues rarely exceeds 100 µm, this almost doubles to 180 µm in tumors, rendering drug penetration ineffective. The result is that less than 0.01 percent of the administered drug gets into the tumor.

What are your hopes for the future of your approach?

SonoTran could be harnessed in multiple ways. As well as heightening the efficacy of a given anticancer drug dose, we could also potentially administer a lower systemic dose, lowering systemic toxicity. This might make certain therapeutics viable for patients who cannot tolerate them at the doses required for efficacy. It could even help salvage failed therapeutics by enhancing the efficacy of these drugs at or below the maximum tolerated dose.

"This first-in-human clinical trial started in January 2022 after nine years of work to get the technology to this point."

Although we are currently focused on cancer, our drug delivery technology could also have potential in other diseases such as atherosclerosis, the major cause of morbidity and mortality in cardiovascular disease, where we would look to get more drug out of the blood vessel and into the plaques.

How did SonoTran improve tumor penetration in the murine test model?

This two-part project was a collaboration between OxSonics Therapeutics and two biopharma companies to assess SonoTran's ability to enhance the delivery and efficacy of an "unarmed" oncolytic vaccinia virus in a murine bladder cancer model.

The initial pilot study evaluated high and low doses of vaccinia virus, which were intravenously administered with or without SonoTran. The results showed that mice treated with SonoTran demonstrated higher viral spread in their tumors at both dose levels than those treated with the virus alone. In the second study, this increase in viral spread in the tumor translated into better efficacy, with 78 percent of mice treated with vaccinia virus and SonoTran surviving to the end of the study versus 56 percent of mice treated with vaccinia virus alone. Both studies showed that SonoTran resulted in a smaller average tumor size and increased the number of responders to the treatment.

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DEPARTMENT

Less Than 5 Percent Human Effort: Thoughts on the Role of Automation on Cell and Gene Therapy

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

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.

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

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Technology

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