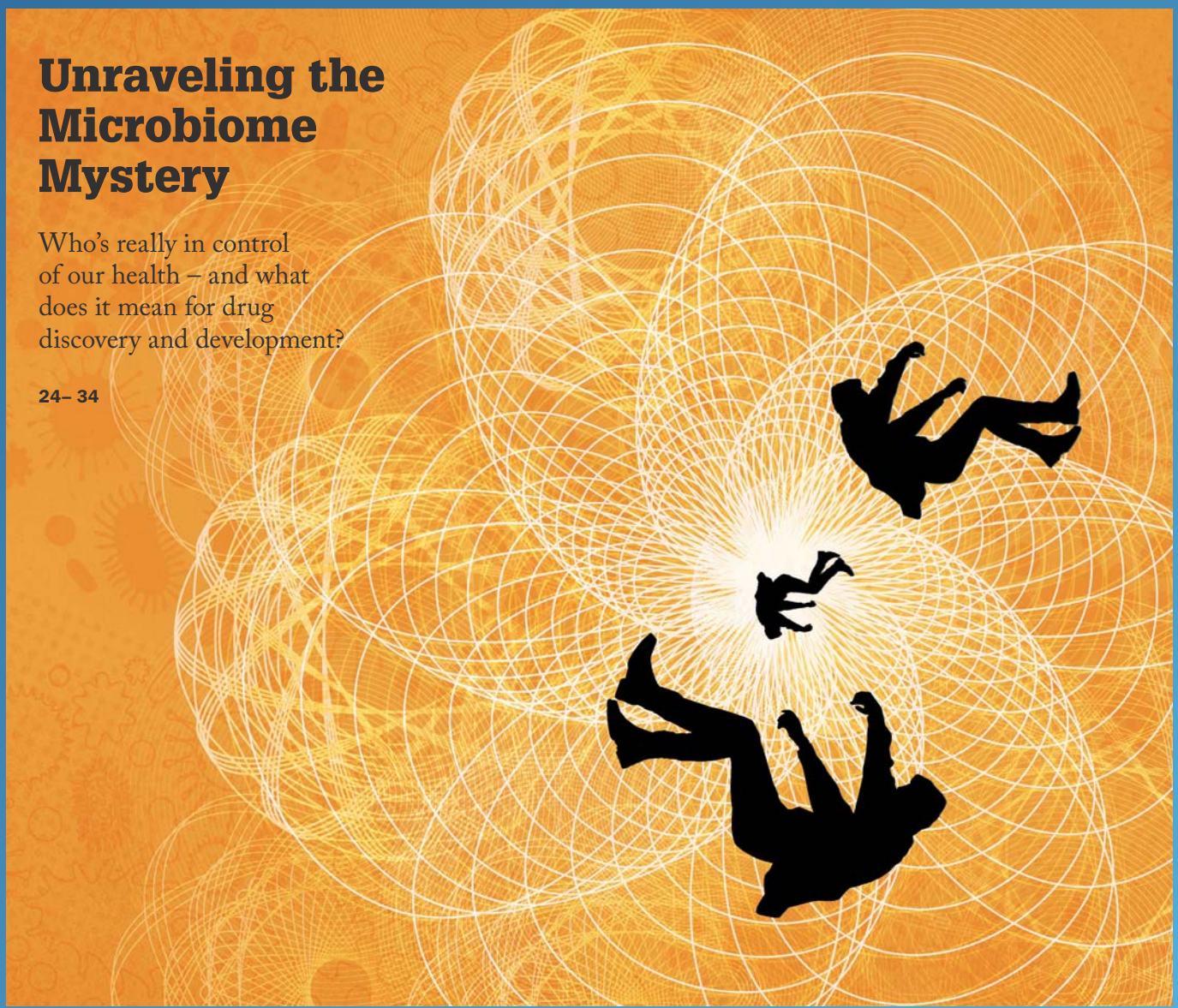
SEPTEMBER 2019 # 57

the Medicine Maker™

Unraveling the Microbiome Mystery

Who's really in control of our health – and what does it mean for drug discovery and development?



An ever-changing journey needs an agile partnership

The dynamic nature of drug development and your world, means you need an adaptable partner. By joining forces with you, we provide a highly flexible, expert service covering contract development and manufacturing services for mAbs and viral vectors, product characterization, biosafety testing and toxicology testing services. So whatever direction your project needs to take, we'll help guide you there.

To find out more, visit:
SigmaAldrich.com/BioReliancePartner

BioReliance®

Pharma & Biopharma Manufacturing & Testing Services

Contents

10

On The Cover

Exploring the complexities – and potential – of the microbiome.

Upfront

the Medicine Maker

ISSUE 57 - SEPTEMBER 2019

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

General enquiries:
www.texerepublishing.com
info@themedicinemaker.com
+44 (0) 1565 745200 sales@texerepublishing.com

Distribution:
The Medicine Maker (ISSN 2055-8201), is published monthly by Texere Publishing Limited, Booths Park 1, Chelford Road, Knutsford, Cheshire, WA16 8GS, UK.
Single copy sales £15 (plus postage, cost available on request info@themedicinemaker.com)
Non-qualified annual subscription cost is £110 plus postage

abbvie

CONTRACT MANUFACTURING

Biologics | ADCs | Potent | Drug Product | Fermentation

Prefilled Syringe | Hot Melt Extrusion | APIs

abbviecontractmfg.com

EXPERIENCE UNRIVALED

Antibody Drug Conjugates

When it comes to biologics, you need a CMO with experience commercializing and manufacturing the market's leading therapy at world-class facilities.

CMO LEADERSHIP AWARDS 2019 CAPABILITIES

CMO LEADERSHIP AWARDS 2019 COMPATIBILITY

CMO LEADERSHIP AWARDS 2019 EXPERTISE

CMO LEADERSHIP AWARDS 2019 QUALITY

CMO LEADERSHIP AWARDS 2019 RELIABILITY

CMO LEADERSHIP AWARDS 2019 SERVICE

Supply Network Redefined.

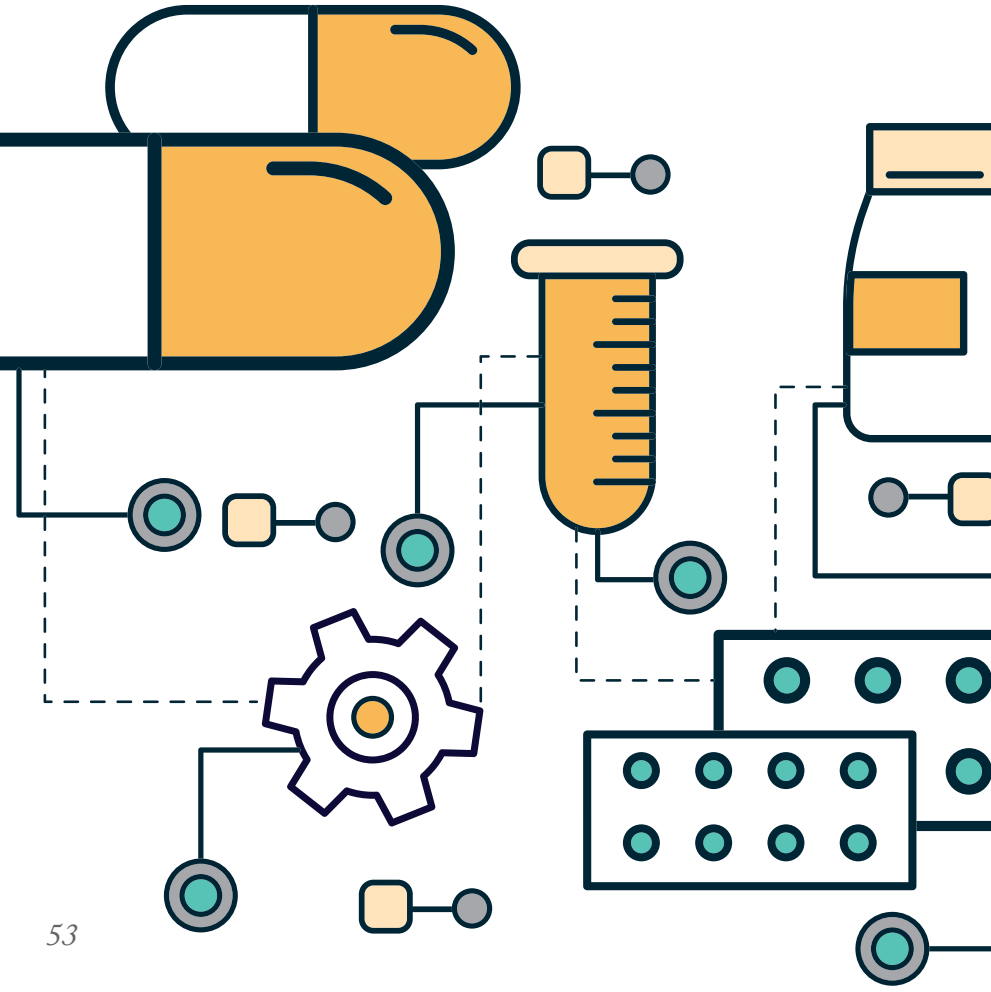
The Foundations for Single-Use Manufacturing. Redefined from A – Z.

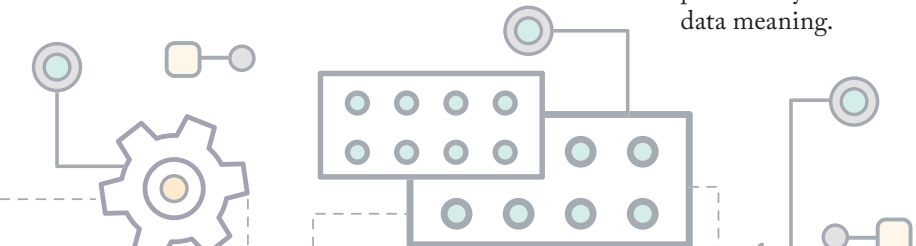
A global manufacturing footprint along with end-to-end process control leads to strong assurance of quality supply.

Benefit from high quality, robust change control and long-term business continuity through our unique supply network.

www.sartorius.com/single-use-redefined

sartorius stedim biotech





TAKE PHARMACEUTICAL DEVELOPMENT TO THE NEXT LEVEL

Rethink what's possible thanks to our 15,000m² first-class facility.

At Arcinova, we unite a diverse range of services and facilities all under one roof. With cutting-edge technology and the best analytical tools to improve productivity, our flexible approach means we quickly adjust to the requirements of every project.

arcinova.com | **@arcinovauk**

ARCINOVA

Redefining Pharma

Should pharma companies transition from developing, manufacturing and pricing "drugs" to promoting "health"?

"The greatest danger in times of turbulence is not the turbulence – it is to act with yesterday's logic."
– Peter Drucker

I've been thinking about this quote recently, and "turbulent" seems like a fair description of the pricing environment facing the pharmaceutical industry today, as governments the world over move to cut healthcare spending – particularly on drugs.

For example, Canada recently announced the biggest reform to its drug price regime since 1987: dropping the US and Switzerland from the Patented Medicine Prices Review Board's (PMPRB) list of countries with which it compares domestic prices (1). Across the border, the Trump administration has taken the first steps towards allowing drugs to be imported from abroad with its "Safe Importation Action Plan" (2). While in China, Pfizer's Upjohn business plummeted 20 percent largely due to the country's volume-based procurement system, which began earlier this year in 11 Chinese cities (3).

How should the industry respond? One option, adopted by Pfizer, is to – almost literally – run for the hills. Earlier this year, the company announced that it would be hiring 600 additional people to drive growth outside the aforementioned Chinese cities (4). Industry bodies will also play their part, lobbying politicians and releasing statements about the "threat to innovation."

But in the context of a global restructure of the drug market, which I think is what we're now seeing, the industry will soon run out of hills. Today's turbulence will require "new logic" – and perhaps a new kind of pharma company.

And when sickness is the norm – three out of four adults in the US are overweight or obese and almost half have pre-diabetes or diabetes, as a recent New York Times blog pointed out (5) – we may see a transition from developing, manufacturing and pricing "drugs" to promoting "health."

Parts of the equation may be value-based payment contracts, open-business models, or partnerships with patient groups – all of which are on the rise (6). But, as others have argued (7), the full solution will take the various healthcare market fragments – prevention, screening, diagnosis and treatment – and combine them to promote overall health.

It's hard for anyone to predict what that might look like exactly; the job of the next generation "pharma" company will be to define the new logic for themselves.

James Strachan
Deputy Editor

References

1. *Reuters, "Canada enacts drug price crackdown, in blow to pharmaceutical industry" (2019). Available at: https://bit.ly/2MQ4bbP. Last accessed August 28, 2019.*
2. *FDA, Safe importation action plan" (2019). Available at: https://bit.ly/2Zn4pk9. Last accessed August 28, 2019.*
3. *Fierce Pharma, "Is Pfizer's established drugs' decline in China the 'canary in the coalmine?'" (2019). Available at: https://bit.ly/2HioDoe. Last accessed August 28, 2019.*
4. *Bloomberg, "Pfizer tries to outrun China drug policy with rural sales push" (2019). Available at: https://bloom.bg/2Zj3uFk. Last accessed August 28, 2019.*
5. *Eye for Pharma, "Deliver patient-centered outcomes to be a trusted partner" (2019). Available at: https://bit.ly/2MHDexE. Last accessed August 28, 2019.*
6. *New York Times, "Our food is killing too many of us" (2019). Available at: https://nyti.ms/2NBHCxR. Last accessed August 28, 2019.*
7. *John Singer, "How to refine strategy and compete on outcomes" (2018). Available at: https://bit.ly/2kuCPSO. Last accessed August 28, 2019.*

Upfront

Reporting on research, personalities, policies and partnerships that are shaping pharmaceutical development and manufacture.

We welcome information on any developments in the industry that have really caught your eye, in a good or bad way. Email: stephanie.sutton@texerepublishing.com

Of Men and Mice

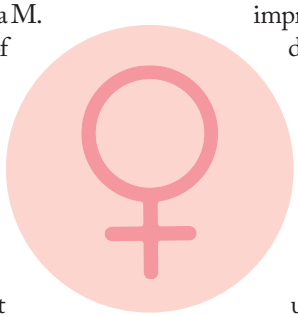
Male animal bias in preclinical research isn't scientifically justified and may be skewing our understanding of the brain

For the past half century, preclinical neuroscience researchers have almost exclusively used male animals. The result? An unclear picture of the neural mechanisms that may underlie disease susceptibility in women – according to Rebecca M. Shansky, associate professor of psychology at Northeastern University in the US.

"Males and females can metabolize drugs differently, so I think if we study only males, we can miss potential side effects that women might experience," says Shansky. "We might also find that drugs don't work as well in females, so it's really important to study both."

In her article for Science (1), Shansky explains that the imbalance is rooted in the belief that circulating ovarian hormones make data from female animals messier and more variable than data from males – a claim refuted by two recent meta-analyses in mice and rats (2,3).

In 2014, the NIH and the Canadian Institutes of Health Research introduced new mandates for researchers to consider sex as an experimental variable, generating a great deal of debate in the research community. And in August, 2019, Senior Editors of the British Journal of Pharmacology followed suit by recommending that all future studies published in the journal should formally address sex as an experimental variable (4).



"I saw the field of neuroscience become concerned that ovarian hormones would complicate their research (which is why they didn't study females in the first place)," says Shansky. "I wrote the piece to help dispel their concerns and ask them to think about why they were under the impression that hormones made data from females more variable than males when that is in fact not true."

Shansky says the reaction has been overwhelmingly positive. "It really seemed to resonate that there were some cultural biases underlying the reasoning for not studying females," she says. "Generally speaking, I think many researchers are coming around to using both sexes. And if they are in the US and want NIH funding, they're going to have to be!"

References

1. *RM Shansky, "Are hormones a 'female problem' for animal research?", Science, 364, 825-826 (2019). PMID: 31147505.*
2. *BJ Prendergast, KG Onishi and I Zucker, "Female mice liberated for inclusion in neuroscience and biomedical research", Neurosci Biobehav Rev, 40, 1 (2014). PMID: 24456941.*
3. *JB Becker, BJ Prendergast and JW Liang, "Female rats are not more variable than male rats: a meta-analysis of neuroscience studies", Biol Sex Differ, 7, 34 (2016). PMID: 27468347.*
4. *JR Docherty et al, "Sex: A change in our guidelines to authors to ensure that this is no longer an ignored experimental variable", Br J Pharmacol [Epub ahead of print] (2019). PMID: 31441038.*

Innovation Deadline

Nominations for The Medicine Maker 2019 Innovation Awards will close on Friday, October 25

The Medicine Maker Innovation Awards were first launched in 2015 to celebrate the top drug development and manufacturing technologies of the year. In our December 2019 issue, we'll showcase the top 15 technologies released throughout 2019 – and readers will also be given the opportunity to vote on the overall winner.

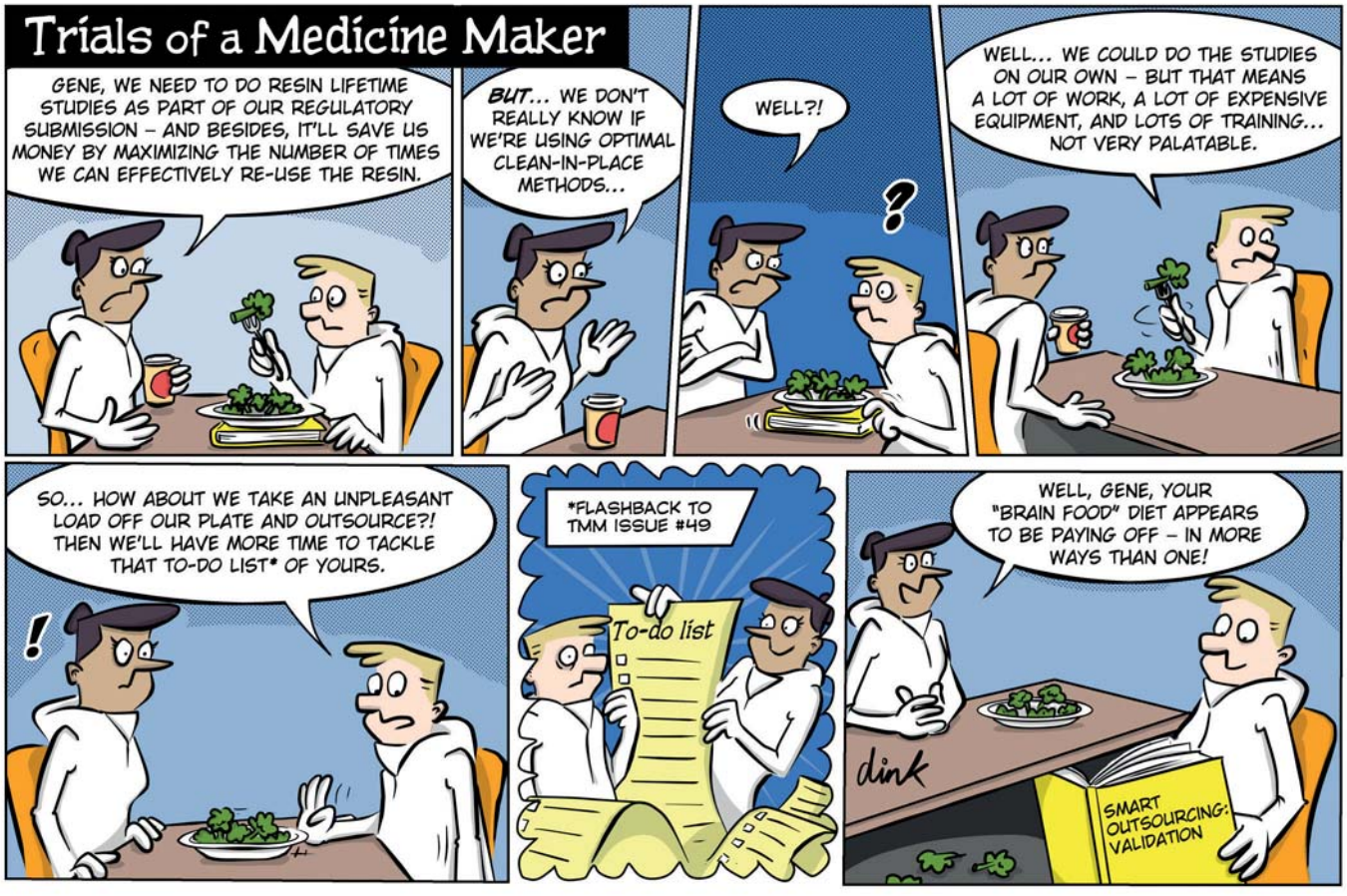
Nominations are accepted from both users and vendors. Users are welcome to nominate the technology they use, while vendors may wish to highlight their latest product launches. The product must have been released (or planned for release) in 2019 and its expected impact on drug development or manufacture should be significant. The innovation can be a piece of equipment, IT software, formulation technology, drug delivery method or any other product or service that you think could fit the bill.

All entries will be assessed but due to the number of nominations received, we only contact companies if their technology is selected to appear in the December issue.

The nomination form is available at tmm.txp.to/innovations19-noms.

Entries close on Friday, October 25. If you have any questions, contact the Editor: stephanie.sutton@texerepublishing.com.

For more adventures featuring Gene and Eva check out our website themedicinemaker.com/additional-data/cartoons
If you have any ideas you'd like to see in future comic strips about bioprocessing then get in touch with us at info@themedicinemaker.com or look up #TrialsOfAMedicineMaker on Twitter.



Brought to you by GE Healthcare

Longer-Lasting Relief

Beyond their symptoms, are chronic rhinosinusitis patients also suffering from a lack of innovation in the ear, nose and throat therapeutic space?

For the 65 percent of chronic rhinosinusitis (CRS) patients who experience a relapse of the condition after surgery and require surgical revision, daily medication to manage the symptoms is a reality. CRS affects between one and five percent of the US population and is defined as the inflammation of the nose and paranasal sinuses. The disease can be sub-categorized into two groups; CRS with nasal polyps and CRS without nasal polyps. Even in cases of successful surgery, patients must continue to take medicines.

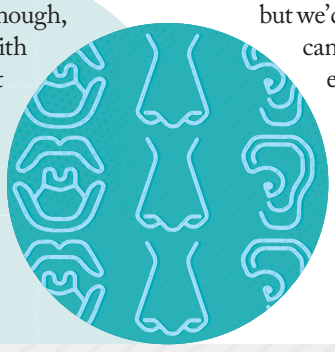
Lyra, a clinical-stage company based in Boston, Massachusetts, is hoping to address what could be considered a lack of innovation in the ear, nose and throat (ENT) space with its lead candidate LYR-210. The product releases a custom, long-acting formulation of mometasone furoate into the intranasal space via a biodegradable polymeric matrix over a 24 week period, alleviating patient symptoms and reducing the need for frequent drug administration.

CRS has been described by the American College of Physicians' ACP Internist as a condition where patients feel "as symptomatically miserable as congestive heart failure and rheumatoid arthritis" but are "consistently ignored". CRS patients are often prescribed steroids to manage their disease symptoms, but topical steroids aren't able to penetrate the sinonasal tissue deeply enough, leaving patients to deal with the pain and discomfort caused by inflammation. And oral steroids, though beneficial, can illicit side effects when used habitually.

"I've always had the mindset of connecting technology innovation with patient needs, and with LYR-210 we have been able to do exactly that," says Maria Palasis, President and CEO of Lyra Therapeutics. "Applying material science concepts enabled us to design LYR-210 to have an effect deep in the sinonasal passages at the site of CRS diseased tissues."

None of the 20 patients involved in the company's recent phase I clinical trial underwent surgery during the 24-week period, and the drug was well tolerated in all patients.

"Our top priority is to make a meaningful impact on the lives of patients with CRS, but we'd also like to explore where we can apply our platform to create effective front-line treatments for other ENT diseases," explains Palasis. "We are also working on LYR-310 for another undisclosed ENT indication. Watch this space!"



Words of a Leader

With 25 years of industry experience and several leadership positions under her belt, we find out what it takes to be a successful repeat entrepreneur from Maria Palasis, President and CEO of Lyra Therapeutics.

Greatest successes?

Without a doubt, the most exhilarating moment for anyone working in biotech is to see your company's product reach patients! I experienced this at Boston Scientific, with the company's first approval for a drug-eluting stent in 2003, which opened the door for our product innovation to reach so many patients.

And I am fortunate enough to have experienced many milestones along our product development path at Lyra! It was a huge moment when we reached the point that our team created a novel therapeutic platform with multiple patented technologies, by merging material science and drug-delivery innovation. It was also very gratifying when we identified the ENT space, and CRS specifically, as an "underrecognized disease" area, where many patients suffer each day.

Best advice?

The advice I give to anyone pursuing a career in biotech is to focus on underserved patient populations and to find a way that your science or technology can make an outstanding product to help these patients. Great leaders in biotech of any gender or background are those who "roll up their sleeves" to create strong business strategies, continuously validate those strategies, and set an inspirational vision to build great teams.

Get Your Coat!

A coating of silica could increase the thermal stability of crucial vaccines

Researchers at the University of Bath, UK, are working on a novel vaccine that uses microscopic silica cases to protect the tuberculosis (TB) antigen and vaccine adjuvant from heat damage. Only one licensed vaccine for TB exists, but variable efficacy, particularly in areas of high disease burden, is cause for concern.

"The main drawback of the Bacillus Calmette–Guérin TB vaccine is that many laboratory strains of the TB virus have lost their "wild" traits that can help trigger our immune system to raise an effective response. So an alternative that can mitigate this issue is needed to help protect patients," explains Jean van den Elsen, Professor of Biochemistry at the University of Bath.

Ensuring the thermal stability of vaccines in the supply chain is essential – but that presents another issue. "Cold chain works well to prevent vaccines from spoiling. However, it relies on having an uninterrupted electricity supply to support supply chain infrastructure," adds Asel Sartbaeva, a lecturer in the Department of Chemistry, also at the University of Bath.

According to estimates by UNICEF program workers, interruptions in supply cold chain account for 40 to 60 percent of wasted vaccines in developing countries, which ultimately leads to more deaths from vaccine-preventable diseases.

The technique developed by a team led by Sartbaeva and van den Elsen is dubbed "ensilication." In essence, it creates a silica coating around individual proteins inside vaccines, preventing them from unfolding. Unlike other encapsulation techniques, the silica coating is a perfect fit – the silica network is grown directly onto proteins, thereby acting as tailor-made protective sheaths.

"The longest experiment we have conducted was about a year long. We observed that there was very little change in ensilicated protein structure when stored at room temperature during this period," says Sartbaeva. "We would need longer experiments to be absolutely sure, but we're confident that the method will increase shelf-life and help reduce vaccine wastage."

The group are now exploring several new avenues for ensilication. They are working on the ensilication of diphtheria and also hope to apply the technique to pertussis (whooping cough) vaccine. The team is also interested in coating bacteriophages. "Bacteriophages are an integral factor in antimicrobial resistance – another global problem. With ensilication we think we will be able to combat AMR in the future," says Sartbaeva.

Finally, it may also be possible to ensilicate antibodies, so they no longer have to be frozen for storage and transportation, opening up a whole other realm of possibility.

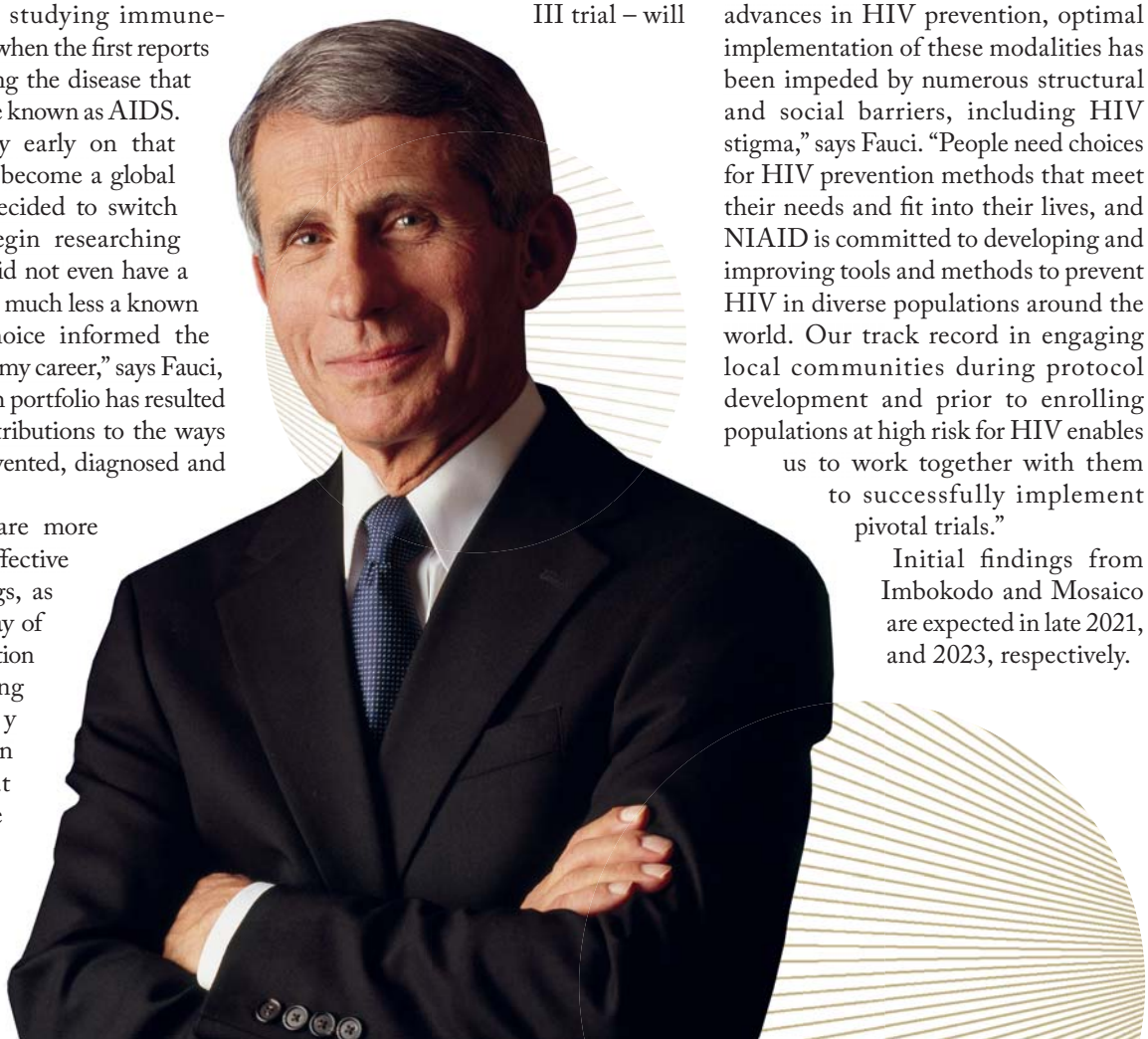
Choice Matters

A mosaic-based vaccine could offer at-risk people more choice when it comes to HIV prevention

Antiretroviral drugs have helped transform HIV from a life-threatening infection to a manageable chronic condition – an advancement that was almost unimaginable in the early 1980s. When Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases (NIAID) at the US National Institutes of Health, first entered the field, the disease didn't even have a name, but he recognized the potential ramifications for the global community. "In 1981, I was in the early stages of a successful career studying immune-mediated diseases when the first reports came out describing the disease that would later become known as AIDS. I recognized very early on that this was going to become a global problem, and I decided to switch my focus and begin researching this disease that did not even have a name at the time – much less a known etiology. That choice informed the entire trajectory of my career," says Fauci, whose vast research portfolio has resulted in substantial contributions to the ways HIV/AIDS is prevented, diagnosed and treated today.

Though there are more than 30 highly effective antiretroviral drugs, as well as a wide array of non-vaccine prevention strategies including PrEP (a daily medication taken by those without HIV to reduce their chances of acquiring the virus), these solutions alone are unlikely to bring about a durable end to the HIV pandemic; vaccines are a much-needed addition to the current prevention toolkit.

Fauci and NIAID have been working with the HIV Vaccine Trials Network, the US Army Medical Research and Development Command, and Janssen on the development and testing of a "mosaic-based" vaccine for HIV, which is made up of elements from different HIV subtypes and uses Janssen's AdVac adenovirus vector platform. It is administered through four vaccinations over the course of one year. It is hoped the two-vaccine regimen will induce immune responses against a wide variety of global HIV strains, including both common and rarely-occurring strains of the virus. The newest study, Mosaico – a Phase III trial – will commence enrolment later this year at multiple clinical research sites in North America, South America and Europe, and will test the efficacy of the vaccine in 3800 in men who have sex with other men and transgender individuals.



A Phase IIb trial (known as Imbokodo) is also currently underway evaluating a mosaic-based HIV vaccine regimen in around 2600 young women, aged 18–35, across five southern African countries.

HIV is challenging from an R&D standpoint because there are no documented cases of people with chronic HIV developing a natural immune response that completely cleared the infection. Enrollment for clinical trials can also pose challenges due the cultural stigmas associated with HIV and sexuality.

"Despite the many valuable scientific advances in HIV prevention, optimal implementation of these modalities has been impeded by numerous structural and social barriers, including HIV stigma," says Fauci. "People need choices for HIV prevention methods that meet their needs and fit into their lives, and NIAID is committed to developing and improving tools and methods to prevent HIV in diverse populations around the world. Our track record in engaging local communities during protocol development and prior to enrolling populations at high risk for HIV enables us to work together with them to successfully implement pivotal trials."

Initial findings from Imbokodo and Mosaico are expected in late 2021, and 2023, respectively.

TAKING A PILL IS AS EASY AS PIE?
50% OF YOUR CUSTOMERS WOULD DISAGREE ...

Visit us at CPhI 2019 in Frankfurt, stand 120D81

A recent study proves that more than half of the population has problems swallowing tablets and capsules. From breaking and dissolving to not taking them at all, people invent their own strategies to cope with tablets – which may reduce efficacy and treatment success.

At HERMES PHARMA, we have over 40 years of experience in making medicines easier to take – from product design through to manufacturing and packaging. If you need support with developing new products that are specifically designed to meet the needs of modern patients, contact us:
www.hermes-pharma.com

Scan QR-code or visit
www.swallowingtablets.com
to get a free copy of the market study.

HERMES PHARMA

Get the dose right®

Eyes on Outsourcing

Catch up on the biggest trends in outsourcing with our infographic

WHAT'S GOING ON IN THE WORLD OF PHARMA OUTSOURCING?

The global pharma CDMO market is projected to reach:

$126.63 billion

by **2024** – up from

$90 billion in 2019

This represents a **CAGR** of **7.1%**

WHAT'S DRIVING GROWTH?

- Rising demand for generics
- Increasing investments in pharma R&D
- Investments by CDMOs in advanced manufacturing technologies
- Increasing demand for biologics
- Advances in cell and gene therapies
- Advances in nuclear medicine

Sources: Research And Markets, "Pharmaceutical Contract Development and Manufacturing Market by Service (Pharmaceutical, Biologics, Active Pharma Ingredients, Tablet, Capsule, Parenteral, Oral Liquid), End User - Global Forecast to 2024," (2019); GEP, "Why Pharmaceutical Companies are Betting Big on Outsourcing," (2019).

WHY OUTSOURCE?

Opportunity for cost reduction – including savings on resources, infrastructure and other overhead expenses

Flexibility

Access to specialized expertise and technologies

Reduced time to market

Popular areas for outsourcing:

- Formulation development
- Analytical and testing services
- API manufacturing
- Clinical trials management
- Solid dose manufacturing

OTHER TRENDS?

Sponsors favor long-term relationships with a small handful of key service providers

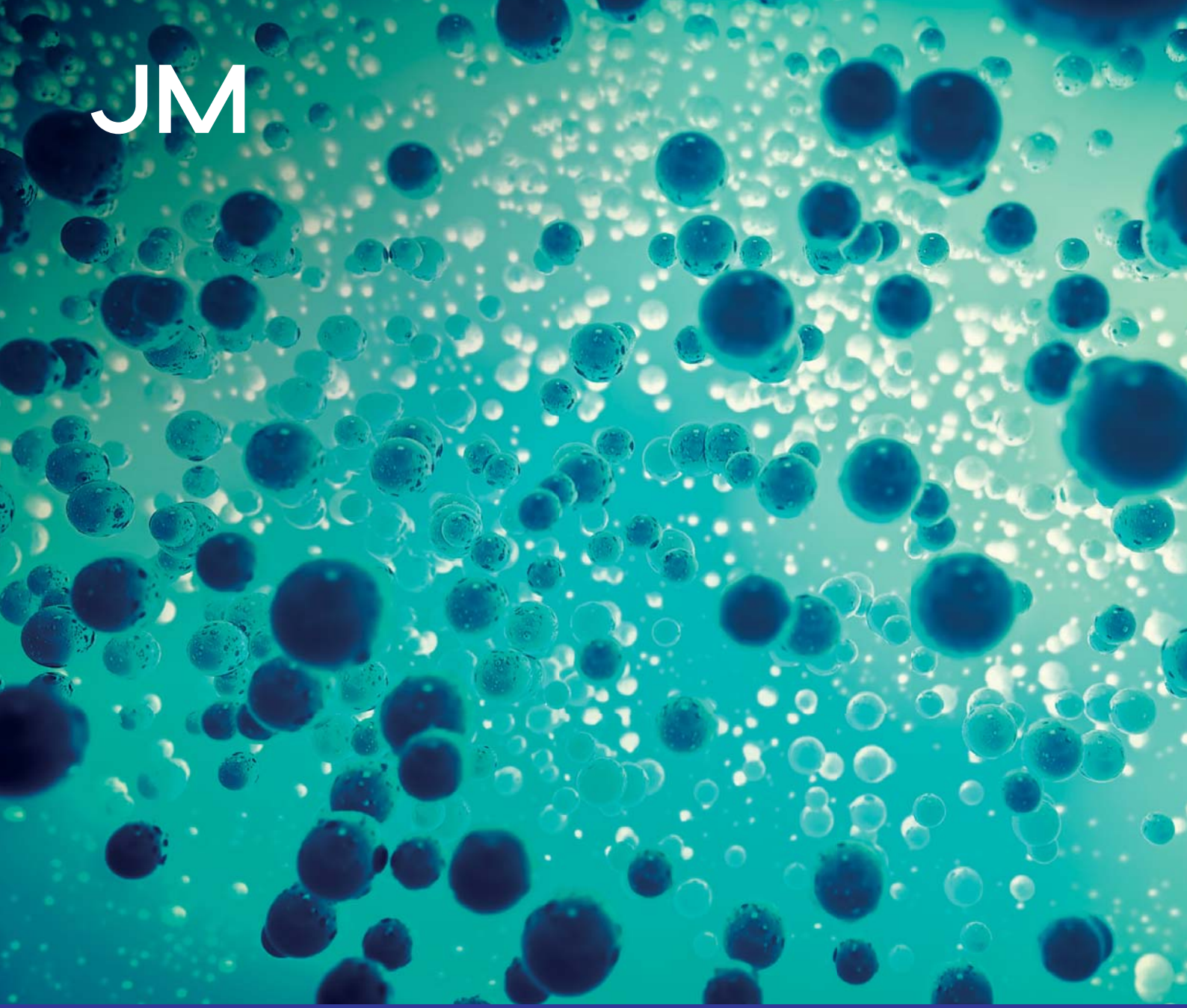
Service bundles and end-to-end solutions are seen to drive efficiency

Regulatory affairs outsourcing is increasing

Prominent players in the market include:

- Thermo Fisher Scientific
- Catalent
- LonzaGroup
- Recipharm
- Vetter Pharma International
- FAMARHealth Care Services
- AbbVie
- Aenova Group
- Consort Medical
- AlmacGroup
- Siegfried Holding
- Boehringer Ingelheim International
- Evonik Industries

Strategic expansions, M&As, and partnerships are a current trend amongst key CDMOs as they seek to expand their manufacturing capabilities and market presence.



JM

Leading biocatalysis capabilities to enhance your molecule development

Biocatalysis is the fastest growing technology for the synthesis of chiral molecules. At JM, we leverage our extensive expertise in enzyme engineering to discover new solutions to accelerate our customers' industrial processes. Together with the chiral capabilities of our chemo-catalyst technology, we offer leading biocatalysis capabilities to enhance your chemistry. Our new range of enzyme kits feature a specialised selection of our enzyme portfolio, comprised of both redox and reductive amination enzymes, providing successful technical and cost-effective solutions to enable your molecule development.

Visit us at CPhI Worldwide, booth 40B30

Johnson Matthey
Inspiring science, enhancing life

To find out more visit matthey.com/biocatalysts or email pharma@matthey.com

In My View

In this opinion section, experts from across the world share a single strongly held view or key idea.

Submissions are welcome. Articles should be short, focused, personal and passionate, and may deal with any aspect of pharmaceutical development or manufacture. They can be up to 600 words in length and written in the first person.

Contact the editor at: stephanie.sutton @texerepublishing.com

Quality Analysis for Life

The data generated by analytical science are crucial to pharma decision-making – so let's adopt a lifecycle management approach to method development to ensure continued excellence.

By Antonio Ramos, Principal Analytical Chemist in Analytical Development at Hovione, and Paula Hong, Principal Consulting Scientist, at Waters Corporation.

For a method to yield reliable, reproducible results over time, it must remain robust throughout the entire lifecycle. The concept of lifecycle management for ensuring the quality of pharmaceutical products is well understood, and has now inspired a relatively more modern concept: method lifecycle management (MLCM). MLCM provides a framework for defining the criteria for and development of analytical methods. Ultimately, this should lead to a more structured and scientific approach to analytical method development (1).

Appropriate and effective analytical methods are crucial for pharmaceutical decision-making because they provide information on the impact of process changes and the quality of pharmaceutical products. As such, it is essential that the quality of analytical methods be assured all the way from development and validation to routine use and transfer. Both CDMOs and pharmaceutical manufacturers should observe the three stages of MLCM:

- Method design and development. Analytical target profiles (ATPs) should drive method selection, design, and development activities, and facilitate continuous improvement of analytical methods.
- Method performance qualification. Confirmation is required to ensure that the analytical procedure is capable of producing reproducible

"Appropriate and effective analytical methods are crucial for pharmaceutical decision-making because they provide information on the impact of process changes and the quality of pharmaceutical products."

data that consistently meet the ATP. This stage should also consider analytical transfer and the implementation of compendial procedures.
- Continued method performance verification. This is necessary to ensure that the analytical procedure remains continuously in a state of control.

In addition, we recommend standardization of instrumentation across multiple laboratories in different locations. Accurate and reliable equipment is integral to MLCM, so advanced technology, such as ultra-high performance liquid chromatography (UHPLC) and mass spectrometry instrumentation, as well as sophisticated chromatography data software, should be considered. In addition, software that can be used across multiple sites to improve information management, storage and data-mining capabilities is essential.

Pharmaceutical regulatory bodies are also pushing companies to enhance their approach to method development by expanding and updating industry regulations. The US Pharmacopeia (USP), for example, has published a series of "stimuli articles" that inform a proposed USP General Information Chapter <1220> "The Analytical Procedure Lifecycle" (2). The articles examine how the modern concept of a lifecycle model, described in the International Conference for Harmonization (ICH) guidelines Q8, Q9, and Q10, can be applied to analytical methods. The article suggests that "the traditional approaches to method validation, transfer, and verification should be integrated into the analytical procedure lifecycle process, rather than being viewed as separate entities".

In addition to the new USP Chapter <1220>, the ICH is drafting two new guidelines: Q12 "Pharmaceutical Product Lifecycle Management" and Q14 "Analytical Procedure Development/Validation" (3). These should provide additional definitions to encourage the implementation of MLCM.

"Pharmaceutical regulatory bodies are also pushing companies to enhance their approach to method development by expanding and updating industry regulations."

In our view, it is important for companies to consider analytical quality by design (AQbD). The concept of QbD is also well known in the pharma industry – so let's apply it to the analytical sphere! Through the application of prior knowledge and an initial risk assessment, AQbD makes it possible to evaluate and prioritize sources of variability that may affect method performance. It helps identify potential issues in the lifecycle and eliminates them based on the method understanding obtained during the development work. In method development, AQbD helps inform which decisions fit the method's purpose and increases awareness of the risks to overcome. Additionally, greater understanding as a result of this approach reduces the number of failures and transfer issues that occur over the lifecycle of the method. For commercial processes, the high quality of data provided by AQbD methods may allow for more timely data release, reduced regulatory risk, and lower costs. The design of experiments is used in data trending and how big data will be evaluated will play an important role in understanding the method capacity to deliver accurate data through its lifecycle. The better the industry's understanding of the impact that changes in method parameters have on the analytical results, the fewer the failures.

Many in the pharmaceutical industry are still skeptical of the changes required to successfully implement MLCM. And, of course, it will take time for people to become comfortable with the concept. But the growing interest in MLCM and AQbD methodologies means that firm regulatory guidelines will likely be in place in the near future – and we believe it's always best to be prepared. The pharmaceutical industry can use this information to improve methods and enhance regulatory flexibility, which will ultimately cultivate a more standardized industry.

References

1. *Waters, "Analytical Procedure (Method) Lifecycle Management Drives Method Development at Innovative CDMO," Available at https://bit.ly/2MyuSr8. Last accessed July 31, 2019.*
2. *USP-NF, "Proposed new USP General Chapter: The Analytical Procedure Lifecycle {1220}," (2016). Available at https://bit.ly/2GBh6AA. Last accessed July 31, 2019.*
3. *ICH, "Final Business Plan; Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management," (2014). Available at https://bit.ly/2Kdra3E. Last accessed July 31, 2019.*

On the Side of Caution

Health and safety matters – particularly in life sciences, where the laboratory harbors many dangers.

By Sue Springett, Commercial Manager at Teknomek.

Risk is a byword for the pharma sector. Though we all know it covers hygiene standards, the safety and well-being of your team are of equal importance. Internal corporate social responsibility (CSR) is high on the executive agenda and there's increasing commercial evidence about the value of being more pedantic when it comes to our employees' welfare. Harming people is expensive – and no-one wants to go to jail...

If we break health and safety down to a cost analysis, it really does pay to look after your staff. As a sector, pharma requires its employees to be, by definition, skilled professionals with salaries above the national average. And that brings about an interesting dilemma. The specialized roles that have been developed to sustain the pharmaceutical industry can be the cause of significant fallout. When inevitable staff absences occur, temporary cover can be difficult to find and the impact on ongoing projects can be significant.

With staff likely to be working with toxic, noxious, or otherwise unpleasant chemicals and items heated to over 100 ^{0}C, health and safety is, by right, a prominent feature in protecting the wellbeing of employees. Regardless of what preventative safety provisions and guidelines you put in place, it's still wise to mitigate risk by preparing for the worst. For example, the cost of installing eyewash stations and showers at strategic points around the lab is going to be much less than a pay-out for an eye injury. It's always better to be safe than sorry – and that goes for all parties. Every second counts when something caustic is in the eye, so having a station within a few seconds reach and easy to use when blinded (and panicked) demonstrates solid due diligence – and provides a strong visual reminder of the due care required from staff.

The same principle applies to autoclaves, regularly chosen for robust sterilization. How are people expected to handle products that have just been sterilized, when touching can lead to burns? You should ensure you have countermeasures and procedures in place to prevent injuries.

Musculoskeletal disorders are the second greatest cause of lost working days in the UK, beaten only by stress and anxiety. Figures from the Health and Safety Executive (HSE) in the UK reveal that the number of days sacrificed to the likes of muscle aches and bad backs totalled £6.6 million in 2017–2018. To cap things off, the average number of days lost per person for these types of conditions was 14 days per year. And that's without counting the so-called "soft costs" of reduced efficiency and management time to address staffing shortages.

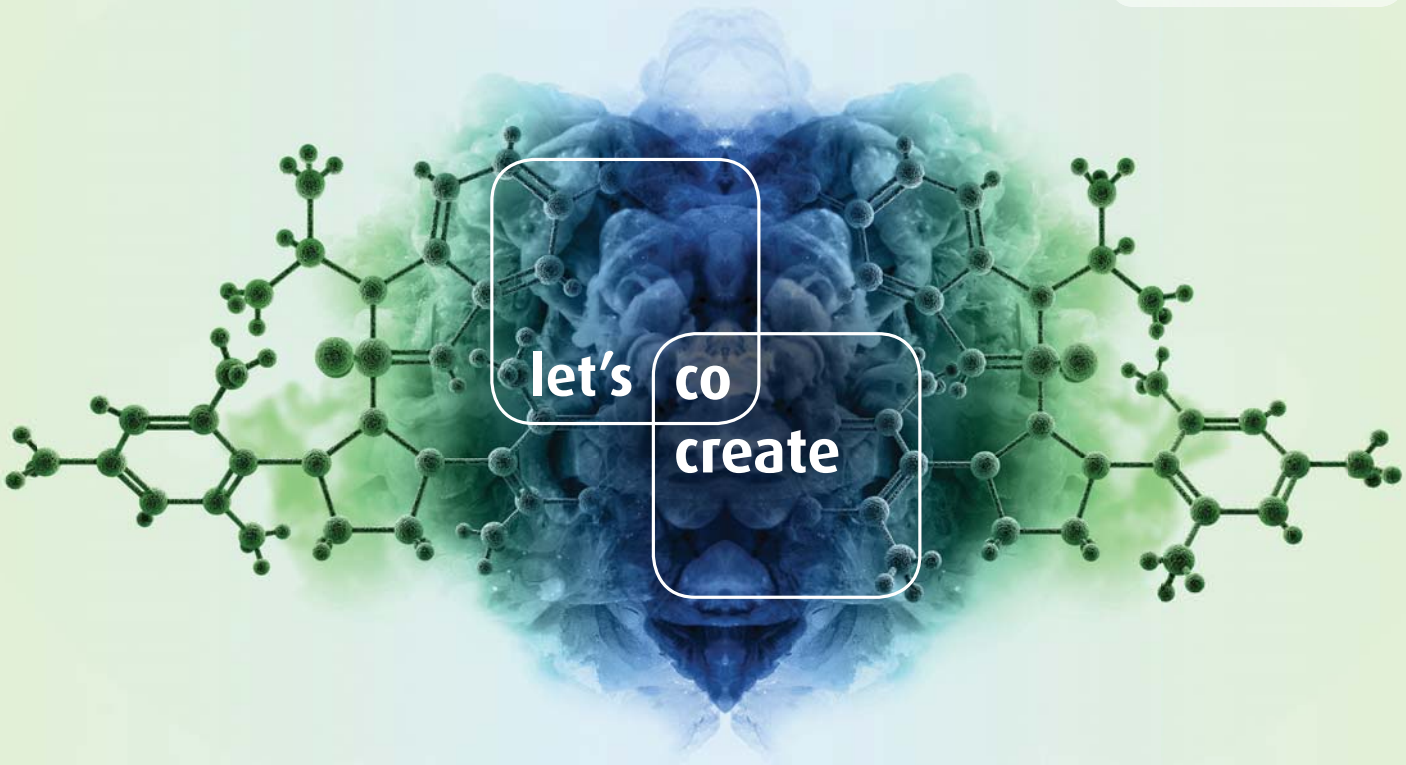
Businesses really can't discount occupational health as simply "nice to have" and it is a sensible move to train up an internal specialist as a healthy workplace champion. Also, bringing in a third-party professional to conduct a workplace assessment is money well spent.

There are some best practices already well-established across the sector. Notably, it's now standard practice to rotate teams across activities throughout the day to minimize the risk of repetitive strain injury. We should applaud such initiatives, but they don't solve the fundamental issue: lab work is usually sedentary and this can be extremely bad for your staff's health.

Over the past few years, I've noticed a distinct uplift in demand for standing tables, height adjustable workbenches, ergonomic seating and anti-fatigue matting. We can't be entirely sure to what extent ordering patterns are the result of proactive decisions to improve health and safety provision, or whether in response to an individual requirement, but there does seem to be a correlation between the uptake and the introduction of the updated health and safety guidelines in many countries. In the UK, for example, updated guidelines on Health and Safety Offences, Corporate Manslaughter and Food Safety and Hygiene Offences were introduced in February 2016. And the average Health and Safety penalty has grown to over £126,000. As fines are aligned to organizational turnover, corporate payouts grew to almost £70 million in 2016–17 – very unhealthy indeed!

Looking at sales trends, businesses seem to be taking the new rules and their responsibilities very seriously. Or our at least our customers are! And we can expect health and safety to creep even further up the corporate agenda given that a whole industry has grown around personal injury.

Visit us at CPhI Worldwide
Booth 80H70



Working together to deliver ground-breaking metathesis chemistry

Driven by our pursuit of innovative and sustainable chemistries, we leverage our global expertise in homogeneous catalysis to bring you the very best in metathesis chemistry.

Our proven metathesis catalysts enable the creation of highly selective carbon-carbon bonds, with high yields and minimal waste, for precise and efficient reactions. We provide cost-effective solutions to your metathesis needs, from research through to commercial scale, offering support in R&D, IP security, global manufacturing and security of supply.

Together, let's co-create to develop the next generation of chemicals for the pharmaceutical and fine chemicals industry.

Let's co-create to make a difference | pmc.umicore.com

materials for a better life

umicore
Precious Metals Chemistry

The Power of Productivity

Tablet coating is not just about aesthetics; a good coat will improve stability, aid patient adherence, and enhance productivity in manufacturing equipment.

By Kelly Boyer

Why is coating important? Aesthetically, a coated tablet looks more appealing, which can impact how a patient feels about their medicine. A well-presented coated tablet, free from defects, gives patients confidence that it's high quality and a trusted product from a reputable company. A coated tablet also provides many important advantages directly to the consumer. Consider patient compliance as one example. An uncoated tablet will often be chalky and, for some patients, unpalatable, since there is nothing to mask the texture or taste. There is also a high chance that the tablet will stick during the swallowing process. If a patient finds taking their medicine difficult or unpleasant then they are less likely to adhere to the prescribed regimen. Coatings can help overcome this issue. For example, we have developed Opadry EZ, easy swallow coating, which provides exceptional slip when the coating becomes wet, making the tablet easier to swallow. This can be particularly important where a large tablet size is unavoidable.

A coating also provides the opportunity for differentiation and prevention of medication mix ups. Some companies choose a simple white coating, but when all tablets look the same there is a higher risk of errors, particularly where patients must take multiple medications. The FDA encourages companies to consider differentiation – especially amongst various dosage levels. Application of a pigmented coating can help to avoid dispensing and administration of the wrong dosage or other look-alike errors. Going back to aesthetics, including color can also make a tablet look more attractive and impart stronger brand recognition.

In addition, coating can convey specific functional properties on to a tablet, such as moisture barrier protection or light protection; and modified release coatings allow the drug release to be delayed or targeted to a specific site.

Reaching for higher productivity

Over the years, film coatings have evolved significantly. The standard coating system traditionally used HPMC (hypromellose) as the main polymer, which is still widely used. HMPC-based coatings provide adequate performance, but there is room for improvement. HPMC coatings may not adhere well to the tablet and are typically slow to apply, resulting in low production speeds. The subsequent introduction of PVA-based coatings gives greater flexibility with improved functionality, providing an opportunity for faster production which in turn means less potential for defects. Most recently, Opadry QX, a quick and flexible coating system, has been developed. Based on a PVA-PEG copolymer system, this coating formulation allows for the highest solids dispersion level, resulting in the greatest process efficiency – some of our customers have reported a 40 to 50 percent boost in productivity by switching to Opadry QX. Buying back machine time can make a huge difference in reducing bottlenecks in production and providing an opportunity to increase coating operations.

We have also evolved from art to science in the area of sugar film coating. Sugar-coated products are very aesthetically pleasing because they have a smooth, glossy surface, with a sweet taste that can mask bitter-tasting ingredients. But the biggest challenge with a sugar coat is productivity and reproducibility. Sugar-coating is a very labor intensive and time-consuming manual process – and the finish, from batch-to-batch, can vary depending on the person performing the coating operation.

"If you purchase a ready formulated coating system then you are buying one material from one vendor, which makes for a much simpler supply chain!"

Bringing in science to bridge the gap, Opadry SGR has been developed. This product is designed to deliver a high gloss, aqueous sugar film coating system that can be used in automated processes (fully perforated or conventional coating pans retrofitted with spray capability), allowing for significant time savings; down from days to a couple of hours.

Ultimately, the coating you choose for your tablet will depend on your requirements. For some companies, high productivity is not possible or necessary, particularly if they are using older equipment, or if labor cost is not a factor. But for others who are running at full capacity, a move to a higher

solids and higher productivity coating may allow them to achieve a greater throughput with their existing assets and delay the need to invest in additional coating equipment.

Coating equipment and geographic location can also dictate choice of coating. It is not uncommon for companies to develop a drug in one region, where equipment and conditions are spot-on, before moving commercial production to another region, where coating equipment may not be as reliable, or where there are issues with airflow, temperature or humidity that present production problems. Choosing a coating which is flexible enough to be used across a range of different conditions while still giving consistent defect-free, flawless coating is a must.

Clean label appeal

A more recent trend that may affect coating decisions is the increasing consumer interest in cleaner labels. Most of this activity is coming from the nutraceuticals industry; in France, for instance, the use of titanium dioxide has recently been suspended for use in food and nutritional supplements, and companies are wary of similar moves in pharmaceuticals and want to get ahead of the curve. In response, we are now actively promoting titanium-free coatings and are getting interest from customers wanting to move to alternative coatings.

Overcome the dangers of "DIY"

Some pharmaceutical manufacturers design and manufacture their own coating, but the majority will buy a ready formulated coating system because it is a simpler, more efficient process than a DIY (do it yourself) approach. Using an in-house coating necessitates the sourcing and associated quality testing of various raw materials from several vendors who may need to be audited and approved. Additionally, inventory will be required for all of these materials, along with dispensing and dispersion preparation operations. Dispensing your own coating materials introduces cleaning considerations and risk for cross-contamination. Creating a stable, consistent coating is not always the easiest process either, especially if you're not a coating expert. Color consistency and uniformity can be significant challenges, as color is contingent on the particle size distribution of pigments and, therefore, any batch-to-batch inconsistency will result in color variation.

If you purchase a ready formulated coating system then you are buying one material from one vendor, which makes for a much simpler supply chain! Plus, the vendor will perform the quality audits of its own suppliers, have second sources of supply and provide regulatory support. It is, however, important to choose a trusted and reputable company. Looking at a company's business continuity plans (BCP) is crucial to ensure reliable supply. Regional manufacturing is becoming an important trend in the pharma industry. At Colorcon, we have seven manufacturing plants located strategically across the globe, which means they can meet the needs of the local market. Importantly, all of our plants are operating with the same raw materials, same equipment and the same processes – and we have done a lot of work to validate the interchangeability of products from all of the sites. If there is an issue getting material from one plant then we can simply supply it from another. We also have technical support laboratories worldwide to help customers through the coating process; enabling them to run trials in our coating labs (they may not have the equipment spare in their own company to run trials), seeking advice from us in terms of troubleshooting, or participating in our "Coating School" training sessions, which cover how best to manage and optimize the coating system.

By partnering with a reputable and trusted company with plans in place to ensure supply, you reap the rewards of a consistent finish developed by coating experts that can also aid productivity!

Kelly Boyer is Film Coating General Manager at Colorcon.

TUNING IN TO *Perfect Harmony*

WHEN IT COMES TO HUMAN HEALTH, WE KNOW THAT GENETICS IS A KEY FACTOR, AS IS THE ENVIRONMENT. WE ALSO RECOGNIZE THE IMPORTANCE OF THE DECISIONS WE MAKE – CONSIDER THE DRIVERS OF DIABETES AND HEART DISEASE. BUT ARE WE AS IN CONTROL AS WE THINK WE ARE? HERE, WE EXPLORE THE PIVOTAL ROLE OF THE MICROBIOME.

By Maryam Mahdi

Microbiome research has not only captured the excitement of the scientific community, but also the general public, who are intrigued by the health impact of the trillions of bacteria that inhabit the various ecological niches of our bodies. Though the microbiome field initially focused on the role of gut bacteria on the onset and progression of C. difficile infection, a wealth of data proving the role of these bacteria in disease indications as varied as Parkinson's and diabetes has begun to emerge; what was once thought of as a disease of the brain may actually be a disease of the gut...

A number of pharma, biotech and start-up companies are now keen to exploit the growing body of knowledge to develop drugs that target the microbiome directly or work in synergy with it to elicit a therapeutic effect – through live bacterial formulations, medical foods, or traditional small molecules. And it may be possible to manipulate the efficacy or side-effect profile of existing medicines by targeting the microbiome. What sets microbiome research apart from other areas of drug R&D is its newness. Companies have the freedom to evaluate and explore the diverse bacterial communities of the gastrointestinal (GI) tract using individual approaches because there is no "right way" of conducting research in this industry.

Here, I speak with passionate microbiome experts who represent just a snapshot of an exciting research community that could transform medicine and drug discovery.

RESTORING THE BALANCE

VENTURING INTO THE UNKNOWN TO HARNESS THE MICROBIOME FOR HUMAN HEALTH.

Young biotech company Rebiotix is using microbiome science to treat GI disease and is involved in a number of clinical trials. Specifically, Rebiotix' Microbiota Restoration Therapy drug platform aims to deliver human-derived microbes into a sick patient's intestinal tract. Here, Lee Jones, founder, president and CEO at Rebiotix, explains how the changing landscape of microbiome R&D is shaping conversations with regulators and helping create metrics for patient norms.

WHAT DREW YOU TO THE MICROBIOME SPACE?

My introduction to the field came through fecal microbiota transplantation (FMT) – the transplantation of fecal bacteria from a healthy donor to a sick patient – to achieve the restoration of a "balanced" gut microbiome. The concept sounded ridiculous to me at the time! I had spent the majority of my career in the medical devices industry and while it was fueled by innovation and progressive thinking, I had never encountered anything so off-the-wall before as harvesting microbes from a healthy person and using them to treat someone who was ill.

But the more I read, the more interesting the concept became. I realized that there was huge potential to help many people through this type of treatment – and that bringing about the success of this type of therapy wasn't really a question of biology, but logistics. Based on my previous experience I knew how to take a product and transform it into something that could be delivered to a patient; I knew how to make a product that could be stored in inventories, invested in, and how to take it through the regulatory process. In 2011, I founded Rebiotix, a biotech focused on transforming the way that GI disorders could be treated using the gut microbiome as the basis of our therapeutics. Our proprietary platform microbiota-based platform – named MRT – uses fecal material from donors to mimic the microbial mix found in the gut of healthy people. These organisms are then subjected to standardized manufacturing processes, quality controls, and stabilization processes with the goal of being able to address unmet medical needs for patients, starting with the life-threatening infection from Clostridiodies difficile, known more commonly as C. difficile infection.

HOW HAS THE FIELD CHANGED SINCE YOU FIRST ENTERED IT?

The world has come a long way from believing that all "germs" are bad; we used to think that we were doing a service to patients by ridding them of these nasty organisms. We've now come to realize that we live in partnership with them. And without many of these microscopic organisms, our health can be severely compromised.

When we first started working on our formulations, there weren't any facilities willing to take on the manufacture of microbially-based therapeutics. No products like this existed in the marketplace, so there was no precedent to follow for facility controls or manufacturing techniques. Without a blueprint to guide their construction, we were breaking new ground in determining how, when, where, and through what processes our products would be made. Rebiotix was the first company to file an Investigational New Drug (IND) application with the FDA for our lead candidate RBX2660, and we needed to hire staff with pharmaceutical, microbiology, engineering, and pathology backgrounds to realize the design of our facility. Like everyone in the industry, their initial frame of reference was to sterilize everything – however, this wasn't conducive to manufacturing a product whose key requirements were to keep organisms alive! It took a significant amount of imagination and creativity to build a facility and develop manufacturing methods for a product line without killing everything off. It was often a difficult process, but we were forced to change our mindset and embrace the learning curve to be successful.

This creative approach and use of imagination has lead us to where we are today. We now have two products in our pipeline; one, an investigational enema formulation (RBX2660), and the other, an oral capsule (RBX7455). Both products are currently under clinical study to address recurrent C. diff infection - RBX2660 is currently in a phase III clinical trial, which, if all goes well, will be the pivotal trial needed to approach the FDA for product approval and ultimately provide us the ability to market this technology.

WHAT IS THE MOST SIGNIFICANT CHALLENGE IN TRYING TO RESTORE THE GUT MICROBIOME?

We share our bodies with roughly 100 trillion bacteria, viruses, and fungi. The challenge for industry is understanding how the proportions of each of these organisms vary between people based on their lifestyles, geographical locations and ethnic groupings. What parameters can be defined as "the norm" when we're all so different? And given the lack of

biomarkers for gut microbiome restoration, how can the efficacy of a treatment be demonstrated when we all have different starting points?

Our Chief Scientific Officer, Ken Blount, has developed a prototype metric for identifying the proportion of bacteria we see in people, and how it changes over time, called the Microbiome Health Index (MHI). The MHI gives us the opportunity to begin investigating the impact of our MRT platform formulations on the gut by assessing the profile of bacterial communities before and after receiving a treatment. Today, we are beginning to use this metric to distinguish between healthy microbiomes and those with dysbiosis (microbial imbalance or maladaptation on or inside the body).

The MHI has the potential to help us and others within the industry demonstrate that gut health is more than a subjective or arbitrary state of being. We hope to show that it is measurable and can be compared with a clinical diagnosis, and, therefore, could be useful in understanding what the next steps in a treatment course may need to be. As the field progresses, we hope to be able to better cater to individual patient needs with an increased understanding of the changes their personal gut microflora undergo over time.

HOW DO YOU SEE REGULATORY FRAMEWORKS CHANGING TO SUPPORT NEW APPROACHES TO DRUG DISCOVERY AND DEVELOPMENT?

Many companies are now pursuing microbiome-derived therapeutics – and working on unique approaches to formulating products to address patient needs. And so, though we may all be in the microbiome industry, no two companies have the same sets of questions or data. The diversity of companies and potential therapeutics gives some within the field a valid cause for concern. What if the regulation that comes into place is too rigid for certain microbiome products and indications?

For that reason, we must ensure that the FDA and biotechnology companies in the microbiome space are on the same page. Rebiotix is a member of the Microbiome

EVERYONE WANTS IN

The potential to revolutionize healthcare through the microbiome is not just a hot area for smaller biotechs and start ups; the field is also attracting some of the pharma industry's biggest players.

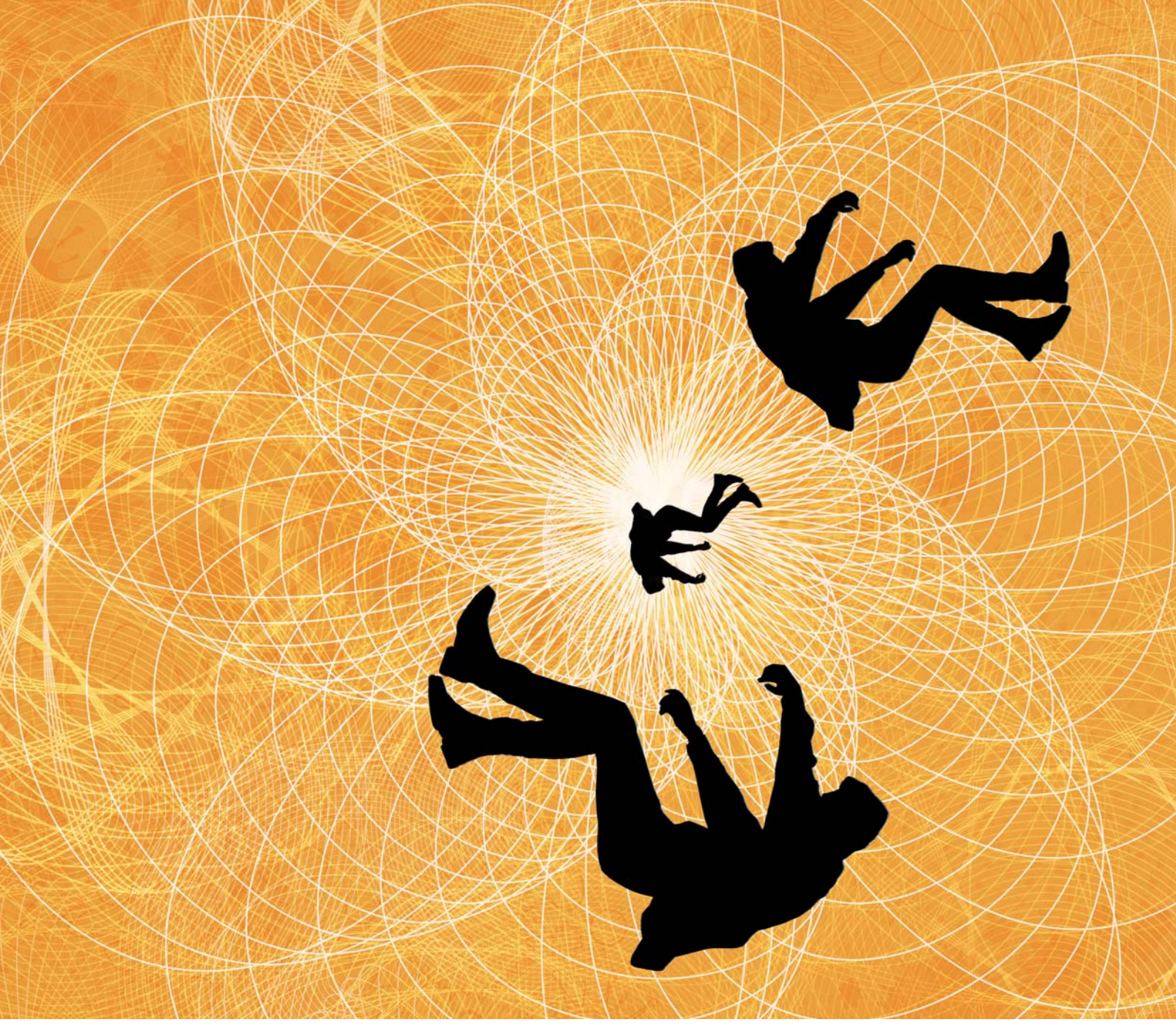
- One of the most active big pharma companies in the microbiome space is Janssen, which has created the Janssen Human Microbiome Institute to accelerate innovation in microbiome science. The Institute works with a number of collaborators – including the University of California, San Diego, Caelys Health, DayTwo Ltd, the Weizmann Institute of Science in Israel, and the Icahn School of Medicine at Mount Sinai – in the development of both micriobiome-based digital diagnostic tools and potential therapeutics. The Institute also works with DNAnexus to sponsor challenges on Mosaic, a cloud-based microbiome informatics platform where researchers can develop, improve, compare, and share microbiome research methods. Janssen is also involved in other microbiome projects and partnerships. For example, in 2018, the Janssen Research & Development entered into a collaboration with BiomX, a microbiome company focusing on phage therapies, to use the company's XMarker platform to stratify responders and non-responders to inflammatory bowel disease (IBD) therapeutics. The XMarker platform uses metagenomics to decipher full microbial genomic signatures, which can then be further developed into predictive biomarkers. Janssen is also working with Vedanta Biosciences on an investigational live biotherapeutic product, VE202, for IBD. "There is significant evidence highlighting the role of the microbiome in the pathogenesis of IBD. Current treatments effectively block mediators of inflammation, but they do not address the underlying alterations in the gut microbiota that may be driving the inflammation in the first place, leaving a need for safe approaches that address this aspect of the disease," said Bernat Olle, Co-founder and CEO of Vedanta Biosciences, in a statement.
- AstraZeneca is collaborating with Seres Therapeutics to explore whether a greater understanding of the microbiome could augment the efficacy of cancer immunotherapies and predict which patients may respond best to treatment. In a statement, Seres said, "Preclinical and early clinical evidence suggests that the composition of the gastrointestinal microbiome impacts clinical response to checkpoint inhibitor immunotherapy and supports the hypothesis that modification of the microbiome may improve outcomes." The partnership will last three years and also give Seres the opportunity to study the effects of its investigational microbiome therapeutic, SER-401, in combination with AstraZeneca's cancer pipeline, which includes checkpoint inhibitors like Imfinzi (durvalumab). The same candidate is also being investigated with Opvido, a Bristol-Myers Squibb checkpoint inhibitor, in metastatic melanoma patients.
- In 2018, Genentech signed a multiyear contract with Microbiotica, a Wellcome-Trust spin out based in Cambridge, UK, to discover, develop and commercialize biomarkers, targets and medicines for inflammatory bowel disease (IBD). Microbiotica will be using its metagenomics microbiome platform to analyze samples from Genetech's clinical trials in IBD to identify microbiome signatures of drug response.
- Finch Therapeutics has stepped into the spotlight after its Full-Spectrum Microbiota therapy, an oral capsule therapy for children with autism, was granted FDA Fast Track designation. Although not a big pharma company, Finch is making headway in the field. According to Finch, studies have shown that individuals with autism spectrum disorder (ASD) commonly suffer from GI symptoms, such as constipation, diarrhea, and abdominal pain. Research characterizing the gut microbiome of individuals with ASD has revealed an abnormal gut microbiome compared to healthy controls.
- CDMOs are also paying increasing attention to the microbiome space. In a joint venture worth €90 million, Lonza and Chr. Hansen are hoping to be among the first CDMOs to create a full supply chain for the manufacture of live bacterial products for therapeutic use. The companies will be focusing on handling, characterizing, formulating, manufacturing and encapsulating strict anaerobic bacteria. Chr. Hansen already has expertise in developing, upscaling and manufacturing bacteria strains, while Lonza will contribute with its capabilities in pharma contract manufacturing, including formulation and drug delivery technologies.

Therapeutic Innovation Group, an independent coalition of companies dedicated to the research and development of FDA-approved microbiome-based drug products to address unmet medical needs, improve clinical outcomes, and reduce healthcare costs. The goal of this coalition is to provide the FDA with insight into the work that is ongoing in the industry and to ensure that all research has patient safety in mind; without the patient and clinical data at the center of development, there would be no way to determine the safest ways to continue to innovate. We have been fortunate to have had several meetings with the FDA, who have assured us that, as long as our research rationales are scientifically viable, they are willing to listen and support this type of work.

In my conversations with other members of the group and the wider industry, I've come to understand that regulators are highly accessible. They, like us, are learning, and therefore it is important for us to continue sharing information and fostering open dialog.

When I first set up Rebiotix, there was only one tool that could be used for sequencing. Few people had considered developing "bugs as drugs" – the idea that microbes could be medicine had yet to capture the public's imagination. But as microbiome research has progressed over the last few years, the number of tools and associated technologies available has exploded. Similarly, though regulation may currently seem scant, it will inevitably develop to meet the needs of the industry.

The microbiome is a source of excitement for everyone. The scientists and clinicians at the forefront of cutting-edge research, the regulators who are helping to shape change, and, perhaps most importantly, the public – the eventual recipients of such therapeutics – have all pushed microbiome research into areas that, until recently, would have been thought of as science fiction. The more steps we take into the unknown, the greater the successes we stand to achieve, and the greater the potential to use this incredible resource to serve unmet medical needs.



FROM CYNICISM TO SUCCESS

SOME HAVE DISMISSED EXCITEMENT ABOUT THE MICROBIOME AS "HYPE", BUT REAL RESULTS ARE BEING SEEN AND MANY NEW THERAPEUTICS ARE IN DEVELOPMENT FOR A RANGE OF INDICATIONS.

With Colleen Cutcliffe

A fourth century Chinese handbook for emergency medicine outlined how FMT can be used to treat food poisoning and diarrhea. Though the ancient manuscript cannot describe the implications of gut microbiota on human health in the way we can today, it does highlight the fact that people have known and believed in the central role of the gut in human disease for centuries. We now have the science to back up the fact that the microbiome is important and can affect our health – and the medicines we take. We now have the opportunity to use emerging knowledge and technologies to fill in the blanks pertaining to the chemical mechanisms of the microbiome and the consequences for us.

Microbiome research is still a relatively new field and in the fledgling years there has been some skepticism about what could realistically be achieved. There were several companies who started out at the same time as our company, Pendulum, and we all faced cynicism. But analytical technologies have helped identify novel targets that could be used to develop interventions for a range of human health issues. Many companies entering the microbiome space initially focused on developing therapeutics for traditional gut-related infections and diseases, but we decided to pursue a different therapeutic area, and started working on metabolic disorders. It is estimated that 415 million people live with diabetes worldwide and we wanted to create options for those patients. Patients with type 2 diabetes (T2D) are often deficient in the bacterial strains capable of metabolizing essential fibers into short-chain fatty acids like butyrate. Butyrate is a small molecule that binds to G-protein coupled receptors (GPCR), which signals for the release of GLP1. GLP1 is a small molecule that enhances the secretion of insulin and reduces blood glucose levels. Without the microbes to metabolize fibrous foods into butyrate, the potential for natural insulin production is lost.

Integrating long-read and high-throughput DNA sequencing, we have assembled genomic-based hypotheses about diabetes, rather than simply categorizing the strains associated with the disease present in the gut. With this knowledge, we have developed our first product designed specifically for people living with T2D.

A double-blinded, randomized, placebo-controlled clinical trial has shown that the product Pendulum T2D Glucose Control is successfully able to reduce hemoglobin A1C (glycated hemoglobin) levels by 0.6 percent versus placebo (for example, from 6.5 to 5.9) and post-meal blood sugar spikes in T2D patients by 60 percent. It's a massive success for the Pendulum team! Not only have we been able to create an efficacious product comprised of naturally-occurring bacterial strains, but we have validated our discovery platform – something our early critics thought impossible.

NO GUTS, NO GLORY

With any novel intervention, the main challenge is determining which pathways and targets will ultimately impact the disease. Is there any value to a therapeutic that offers nothing new to patients? The answer is obvious. Companies developing microbiome-derived therapeutics not only have to tackle this issue but the fact that there are very few tools available for their production. The tools available for the creation of traditional drugs are the product of decades

REGULATORY ACTION

The myriad options available to companies looking to develop microbiome-focused therapies is exciting, but it is also a double-edged sword. The development of bacterial-based therapies comes with significant manufacturing challenges. Can sufficient quantities truly be produced to influence a community of trillions of microbes? With FMT requiring donor screening to ensure quality and consistency and further implications for companies working with genetically modified bacteria, the budding regulatory landscape for these types of products is already proving to be difficult to navigate.

Kaleido Biosciences is pursuing small-molecule drugs through novel chemistry to modulate the metabolic output and profile of the microbiome. Their lead candidate, KB195, is currently in phase II development and has the potential to be used for urea cycle disorders. Because KB195 is a small molecule drug, manufacturing is a relatively straightforward, transferable and scalable process. A live bacterial product (LBP) is a product (other than a vaccine) that contains living organisms intended to treat human disease. Probiotics are similar in that they contain living organisms. Although probiotics are legal, in most countries they cannot be marketed to cure or prevent disease. While, Kaleido's candidates are not LBPs, Susan Stewart, SVP, Regulatory Affairs & Quality at the company, understands the challenges that companies pursuing LBPs may face in seeking a solid regulatory framework.

"Our microbiome metabolic therapies are regulated by CDER at the FDA, and so our early development can follow regulations covering Generally Recognized as Safe (GRAS) compounds under Food Law, and drug products under Drug Law when pursuing therapeutic indications," Stewart says.

But the FDA isn't ignoring LBPs. The Agency has hosted public workshops to address the rapid advancement of LBPs into late-stage clinical trials and to allow the industry to voice its concerns pertaining to manufacturing and regulatory affairs for microbiome-derived therapies. "The FDA has shown a willingness to advance this new medical target as is shown by its position on the development of LBPs as biologics under INDs and its specific exemption for fecal microbiota transplant for treatment of recurrent C. difficile infections by clinicians." explains Stewart.

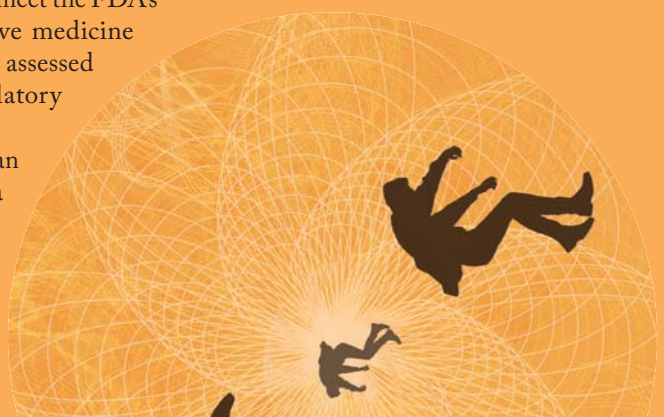
The FDA released its first guidelines on the regulation of live biotherapeutics for clinical trials in 2012, which included definitions and examples of accepted assays for purity, potency and stability; the guideline was updated in 2016 (1). Some industry experts have argued that that LBPs should be regulated under the same guidelines that govern the approval and manufacturing of tissue transplants, but because LBPs do not meet the FDA's definition of regenerative medicine therapies, they cannot be assessed under the same regulatory framework.

In Europe, the European Pharmacopoeia Commission has set the quality requirements for LBPs with a monograph on "Live biotherapeutic products for human use (3053)" and two general chapters, "Microbial examination of live biotherapeutic products (LBP): test for enumeration of microbial contaminants (2.6.36)" and "Microbiological examination of live biotherapeutic products: test for specified microorganism (2.6.38)." The texts became effective in April 2019 (2). These specifically exclude FMT and products intended as gene therapy agents.

A significant number of clinical trials for microbiome products are now well underway and Stewart is confident, particularly in the US, that regulatory support for all aspects of microbiome drug development exists. She says, "positive late-stage clinical data for microbiome therapies in development will be critical for the advancement of the entire field."

References

1. *FDA, "Guidance Document: Early Clinical Trials With Live Biotherapeutic Products: Chemistry, Manufacturing, and Control Information; Guidance for Industry" (2016). Available at https://bit.ly/2ZfWGs6. Last accessed August 27, 2019.*
2. *EDQM, "Live Biotherapeutic Products (LBPs): European Pharmacopoeia Commission sets unprecedented quality requirements," (2018). Available at https://bit.ly/2MDXQH5. Last accessed August 27, 2019.*



worth of enhancements and innovation. They suit the needs of conventional drug development and manufacturing. The newness of the microbiome means that companies must figure out the essentials of building a lab and how to manage the challenges that come with logistics. How can partners in the supply chain help get products from A to B? As our T2D product contains live strains of bacteria, a robust cold chain strategy must be enforced to ensure that people receive quality products.

Patient education is also an important consideration for pharmaceutical companies. Though people are increasingly aware of the microbiome and its implications for human health, have we educated them enough to truly understand what the field has to offer? Do they know the difference between a microbiome-derived small molecule, FMT, a probiotic, a prebiotic, and a medical food? Are they aware of the risks of "do-it-yourself" treatments? There is a constant stream of information that people are able to access through the Internet and social media, and while it is positive that patients are engaging with this area of research, it can be difficult to understand everything that is happening in the field. Patients are certainly receptive to microbiome research and are looking for solutions to their medical problems; therefore, from a commercial standpoint, we must make sure that we help patients understand what a product can (and can't) do and what value it may add to the management of their disease.

Patient excitement mirrors our own. Companies are creating solutions that go beyond traditional medicine making, and in the next five years we could see microbiome-based therapeutics for GI disorders, metabolic syndrome and CNS disorders becoming part of the pharmaceutical landscape. The link between nature and science has always been a point of discussion, but for the first time in history we have the tools to truly marry the two together.

We should all be prepared to stand in awe of the new wave of innovation that microbiome products stand to offer!

Colleen Cutcliffe is CEO and Co-Founder at Pendulum.

IT'S ALL CONNECTED

IF THE SCIENTIFIC COMMUNITY WANTS TO TACKLE NEUROLOGICAL DISORDERS, IT NEEDS TO SHIFT ITS FOCUS BEYOND THE BRAIN – THE GUT ALSO PLAYS A ROLE.

Do neurological disorders begin in the brain or elsewhere? Mounting research now points to the enteric nervous system (ENS) – our second brain – in the onset of central nervous system (CNS) disorders like Parkinson's Disease (PD). The ENS has an extensive connection to the brain and is integral to gastrointestinal function. Some biotech companies, such as Axial Biotherapeutics, are beginning to explore the gut-brain axis for the development of novel therapeutics for diseases and disorders affecting the CNS. Axial was founded in 2016 to pursue non-traditional approaches to treating CNS diseases by targeting the gut rather than the blood-brain barrier to treat disease.

"The direction in which we took the company went against the doctrines taught in medical schools for decades, i.e., treating CNS diseases by developing systemically available drugs that cross the blood brain barrier," says David H. Donabedian, co-founder and CEO of Axial Biotherapeutics. "Today, we have a pipeline of candidates that target the gut and the gut-brain axis, contrary to these mainstream approaches."

Axial believes that certain diseases, e.g., PD and Autism Spectrum Disorders (ASD) may emanate via the gut and the gut microbiome. Since 2015, approximately 15 publications have established that the PD microbiome is different from matched healthy controls; and certain types of bacteria are elevated in the PD microbiome. In PD, many non-motor symptoms, including constipation, loss of smell (hyposmia) and trouble swallowing (dysphagia) precede motor symptoms by years. Braak's hypothesis helps explain the connection between the gut and brain and resulting disease progression in PD. The hypothesis states that pathogens enter the body via the nasal cavity, reaching their final destination in the gut where they cause the aggregation of abnormal proteins, Lewy bodies, in nerve cells contributing to sporadic PD, the most common form of the disease. The buildup of Lewy bodies also impairs the enteric nervous system resulting in changes in gut transit time, which can lead to unpleasant non-motor symptoms, including constipation, dysphagia and hyposmia.

"The gut microbiome promotes the normal development of the ENS and may help modulate GI function," explains Donabedian. "The resident microbiome can, therefore, influence host homeostasis and, when unbalanced, may trigger the non-motor symptoms experienced by PD patients."

Axial's lead candidate, AB-4166, is a small molecule drug that stops Lewy body aggregation and is currently being evaluated for safety and tolerability in a subset of PD patients. Axial's PD program has also identified multiple novel chemical entities in the AB-4000 series which are being developed to have improved selectivity as potential next-generation drug candidates for PD and other neurodegenerative diseases.

In addition to PD, Axial is interested in the microbiome's ability to influence ASD. The company is focused on understanding the role of microbial based metabolites in specific ASD patient subgroups. Though it is understood that we all are different and therefore have differences in our gut microbiome and microbiome-based metabolites, when compared with neurotypical children, certain ASD children tend to have less overall abundance and diversity in their microbiome, which results in an altered microbiome-based metabolite. Donabedian explains that this change may be attributed to many factors, including a leaky gut phenotype. A leaky gut may allow for certain molecules to pass through the GI tract that normally would not have access and may also allow oxygen to enter the gut and alter the resident microbiome profile, further exacerbating GI symptoms like diarrhea, constipation and abdominal pain.

Axial has developed, AB-2004, a gut retentive small molecule that has demonstrated, in animal models, the ability to repair leaky gut and improve repetitive behavior, anxiety, and ASD-related sensorimotor gating deficits by removing key microbial metabolites. "Our preclinical studies and cross-sectional data in ASD children support that certain metabolites are overrepresented in subsets of autistic children," says Donabedian.

Regulators are keen to support companies who are developing microbiome-targeted small molecules. Unlike companies chasing fecal microbiome transfer approaches, which pose unique challenges for regulators because they are so different to traditional drug products, such companies are creating small molecules with similar characteristics to those already used for the treatment of CNS disorders.

FUTURE OUTLOOK

Axial recently announced a collaboration with Taiho, a Japanese pharmaceutical company focused on the development of treatments for cancer. The partnership will give the Japanese company access to Axial's platform for the discovery and development of novel compounds for oncology therapeutics. Though therapeutics like immunotherapies are massively changing patient outcomes, these outcomes are often heterogeneous, and existing biomarkers do not accurately predict patient response. Microbiome-targeting therapeutics for oncology offer the pharmaceutical industry new ways to combat cancer and may be manipulated to better fit patient needs.

Lonza

Lonza Engine™

Accelerate Innovation

Liquid filled hard capsules filling and sealing equipment

Micronization equipment

Powder micro-dosing system

Made better. By science. ™

Want to know more?
Visit www.capsugel.com

The Holistic Approach to Upstream Viral Safety

There could be significant benefits to implementing additional measures in upstream bioprocesses to prevent viral contamination. But, given that upstream processes are complex, multiple strategies and technologies must be integrated within a holistic risk management program.

By Craig Jackson and Michael Cunningham

When it comes to viral safety, biopharma companies have historically focused on their downstream processes, but recently there is increased awareness of the potential disruption viral contamination can bring, and a move towards mitigating the risk in upstream cell culture processes. The key driver for all aspects of viral safety is, of course, patient safety, and there are few regulatory pressures pushing companies to incorporate viral risk mitigation technologies upstream. Regulatory guidance focuses on ensuring cell lines and raw materials are well-characterized and free from detectable adventitious agents. However, there is a good business case to implement measures that minimize the risk of viral contamination and the potential disruption to manufacturing operations.

Where can contaminants enter the upstream process? Chinese hamster ovary (CHO) cells are especially susceptible to contamination with rodent viruses; minute virus of mice (MVM), in particular, has led to problems at a number of biopharma plants. Contamination often originates from raw materials and animal-derived components such as bovine serum or trypsin, which are regarded as particularly high-risk. Contamination can also originate from other cell culture components such as glucose – which attract rodents – or from equipment or facility operators, who can introduce human virus contaminants (such as adenovirus) into a process (Figure 1, viral risk identification).

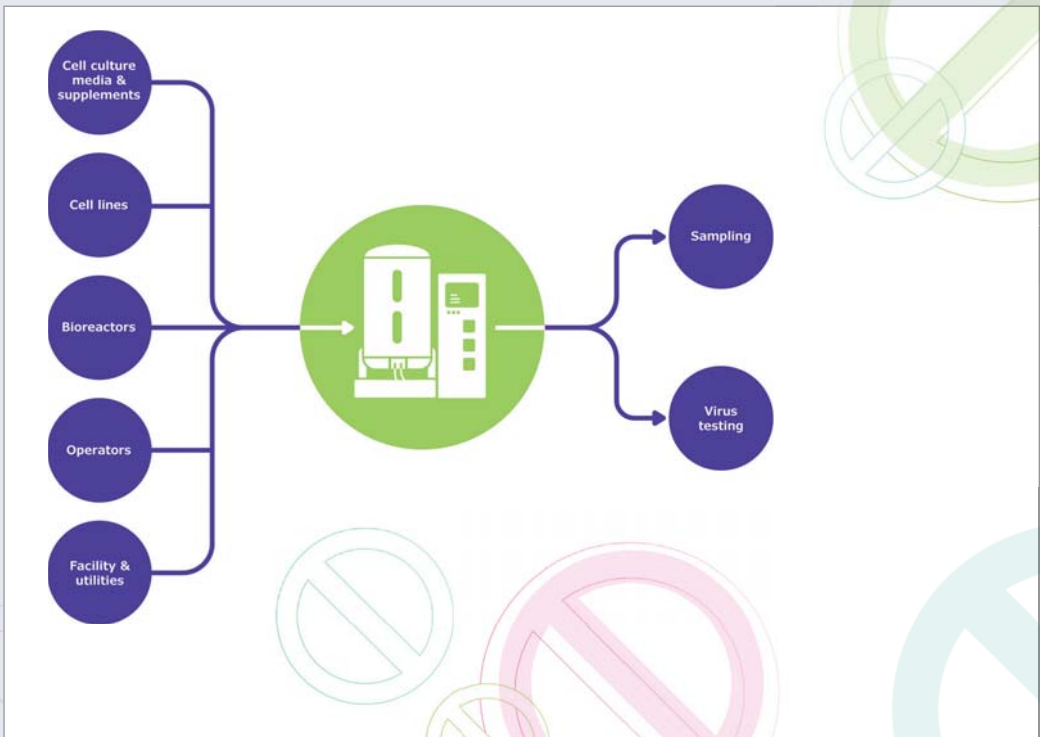
Multiple lines of defence

The multitude of potential contamination sources necessitates a risk mitigation strategy built on complementary elements that prevent contamination and include both the raw materials and the manufacturing environment (Figure 2, viral risk mitigation strategies upstream).

A recently introduced option to reduce contamination risk is the availability of genetically modified CHO parental cell lines that have been engineered to eliminate the receptors used by the virus to enter cells, rendering them resistant to MVM infection. More traditional approaches for raw materials focus on sourcing, selection and treatment. Wherever possible, animal-derived cell culture components at high risk of virus contamination should be replaced with lower-risk alternatives, such as non-animal origin supplements, or recombinant proteins where the production processes reduce concerns about adventitious agent contamination. Where animal-derived components must be used, they should be carefully sourced from lower risk geographies. However, no material, even plant-derived or of recombinant origin, should be considered risk-free, as contamination may occur at any time throughout the supply chain of the raw material.

An additional virus risk mitigation option is to treat raw materials to inactivate potential viral contaminants before they enter the manufacturing facility - a "point-of-origin" strategy. For instance, bovine serum can be treated with gamma irradiation to inactivate viruses, and glucose can be treated with high-temperature short time (HTST) pasteurization to inactivate viruses – even those with high physico-chemical resistance. The recent availability of HTST-treated glucose manufactured under an ISO9001:2015 comprehensive quality management system is a new option for biomanufacturers, which may

Figure 1: Viral risk identification is a prerequisite to a viral safety strategy.



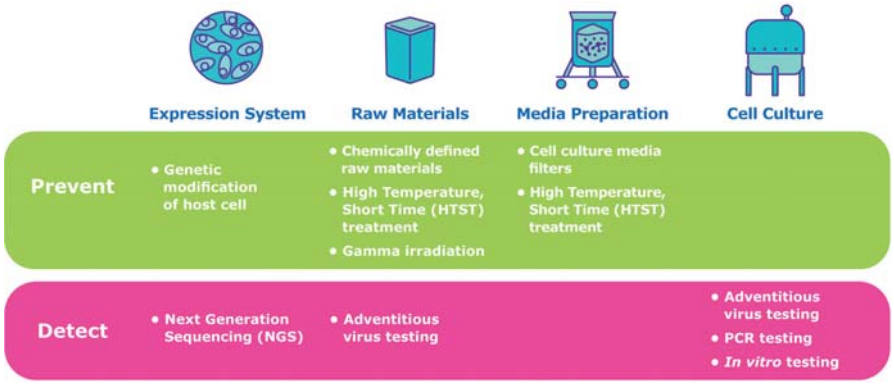


Figure 2: Viral risk mitigation strategies upstream use diverse technologies, such as detection methods of viruses in cell lines and raw materials, treatment and filtration of raw materials, and cell line engineering.

eliminate the need for significant capital investment and establishment of HTST technologies in-house.

In addition to "point-of-origin" approaches, the risk of viral contamination of cell culture processes can be reduced by implementing "point-of use" strategies that focus on treating materials immediately before they are used in the bioreactor. Filtration and HTST treatments of cell culture media are examples of point-of-use strategies that remove or inactivate potential adventitious organisms from cell culture media preparation. The recent development of virus-retentive filters specifically designed to process cell culture media offer additional benefits to traditional sterilizing-grade filters for reducing the risk of introducing viral contaminants into the bioreactor. These filters efficiently process many different cell culture media, while delivering high retention of viruses and mycoplasma and sterilizing-grade performance for bacteria, all with low capital investment.

Perhaps the most effective approach to prevent contamination is to work with suppliers who follow high quality standards with transparency and visibility of their supply chain. Understanding the origin of raw materials and how they are controlled in a quality management system provides peace of mind.

The rise of real-time detection

Although there are several good options to reduce the likelihood of virus contamination, risk cannot be entirely eliminated. All comprehensive virus risk reduction strategies depend on a sensitive panel of virus assays capable of detecting contamination if it is present. Regulatory guidance documents provide a detailed framework of testing expectations for biologic products.

Traditional cell-based assays remain the standard approach to biosafety and viral testing, but biopharma manufacturers are increasingly being drawn to newer molecular methods, such as broad specificity polymerase chain reaction (PCR) and next generation sequencing (NGS), to expedite the viral safety testing process. These newer testing strategies can provide greater confidence in viral testing results and opportunities to accelerate testing.

Bioprocesses are also evolving – and connected, continuous, intensified, and more automated processes present some particular challenges to minimizing contamination risks of viral contamination. For example, the high media requirements for intensified processes increases the possibility of viral contamination. In addition, because steps are linked together, problems can ripple through the process – potentially to downstream operations. These challenges are best met with technologies that enable rapid, real-time monitoring of the upstream process.

Finally, it is also worth drawing attention to the advantages of implementing single-use technologies in upstream processes. Single-use technologies such as bioreactors, connectors and sampling devices are pre-sterilized with gamma irradiation before use, reducing the risk of introducing contaminants into the operation. In addition, if contamination occurs during processing, contaminated material and components can be rapidly disposed of. Single-use technologies eliminate much of the cleaning that might be required in the event of contamination in more traditional stainless-steel systems, enabling manufacturers to get back on-line faster. In an industry where time is money, single-use systems and components offer both flexibility and other advantages to manufacturers.

Staying safe

Traditionally, preventing upstream viral contamination has focused on sourcing and testing raw materials. This approach to risk mitigation has worked well for many years and, to date, no contaminated biopharma products have reached a patient. For manufacturers, however, viral contamination events are incredibly disruptive and expensive; high-profile cases are driving companies to re-examine their risk assessments around virus safety and take steps to reduce risk upstream of the bioreactor.

There is no single viral safety solution that works for every process – solutions depend on the process, media components, facility, scale, and the type of biologic being produced. Multiple strategies and technologies to mitigate risks should be integrated into an overall virus safety management program – based on effective risk analyses. In short, a holistic approach that considers all components of the manufacturer's process, is the only reasonable approach to minimize pathogen safety risk.

Craig Jackson is Senior Account Manager, and Michael Cunningham, PhD, is Associate Director, Upstream Global MSAT, both at Merck.

NextGen Now.

DELIVERING TOMORROW'S FACILITY, **TODAY.**

ENGINEERING | ARCHITECTURE | CONSTRUCTION | CONSULTING

NextGen

R&D pipeline
New technology
Future trends

Giving Data the Gift of Meaning

Ever-growing datasets are a constant challenge when trying to develop efficient clinical trials. As more conventional approaches fail to give companies the competitive edge they need, can the insight provided by predictive analytical tools pick up the slack?

By Gen Li and Jonathan Peachey

An underpinning value of the pharmaceutical industry is its desire to provide solutions where there seem to be none – and yet each year the pharma machine continues to churn out drugs, which, rather than being first-of-kind treatments to combat areas of unmet need, are often alternative formulations of existing products. Despite the millions of dollars annually spent on R&D, true scientific breakthroughs seem few and far between.

Big data has become an industry buzzword – and could be particularly useful for improving clinical trials. The industry knows that big data has huge potential but pharma companies are inundated with data from various sources, which is often found in different formats and grows at an incredible velocity. Selecting data that will significantly impact the quality of clinical trials and result in breakthrough medicines is more than a trying task.

While trials are intended to be high quality, transparent, and discoverable, companies are often at a loss as to how to handle the vast amounts of data available to them. The large volume of structured and unstructured information companies encounter can significantly reduce the visibility and discoverability of pertinent data as making true comparisons between trials can become a virtually impossible task when handled manually. And the problem is only exacerbated by the rapid rate at which datasets grow.

Clinical trials are also plagued by other issues:

- Poor recruitment. Investigators often overestimate their ability to recruit suitable patients to trials. In some therapy areas, there may be smaller populations of patients for certain indications and public awareness can also be poor, resulting in fewer people engaging with the recruitment process. Strict exclusion criteria can also hinder recruitment.
- Misinformed site selection. Trial sites should have sufficient resources and experiences to effectively manage a trial. A proven history of performance in similar studies is important, but does not guarantee that each site will perform well in every trial. The lack of detailed guidelines and lack of due diligence done to inform site selection can result in trials set up with the wrong number of sites, in the wrong geographies. The systematic reviews required to ensure that the best sites are chosen can often fail to take place.
- Patient burden. Clinical trials can be an inconvenience to patients. Patients must commit themselves

MERCK

Pellicon® Capsule

EXPLORE SIMPLICITY

- Single-use TFF for fast and flexible product changeover
- Ready to process mAbs and ADCs in minutes
- Enhanced product and operator safety

Let's Explore What's Next at
MerckMillipore.com/Explore

MK_AD1870EN ver. 1.0

The life science business of Merck operates as MilliporeSigma in the U.S. and Canada.

Millipore®

Preparation, Separation, Filtration & Testing Products

Meet Phesi

The company?

Gen Li: Before creating Phesi, I'd been in the industry for a long time, and one of the biggest frustrations for me has always been the uncertainty of the clinical development process: uncertainty in terms of the time frame and costs. You anticipate that a trial will be short and not too expensive, but as soon as you start the picture can change quickly. The pharma industry invests huge amounts into R&D and we need some sort of structure to see through the data noise and identify patterns.

This motivated me to create Phesi and to focus on AI and data-driven products and services. And we are making good progress in terms of analyzing data and transforming that into knowledge that can be used to make important clinical trial decisions. Do we know everything? No, but we now have an effective way to look at some very important issues associated with the clinical trial process and identify the fundamental reasons behind these.

The focus?

Jonathan Peachey: We are trying to use predictive analytics to provide more certainty in an unpredictable world. It is not the pharma industry's fault that it is struggling with internal challenges around data. What data do I need? How much data is there? What is relevant? How do I act on it?

Gen was the visionary behind Phesi. I'd been working in parallel at the time with IBM, who were thinking about IBM Watson, and smart analytics and smart planners. I met Gen and I was impressed because he demonstrated the benefits in speed and cost that could be achieved by harnessing data.

Throughout my time working with Gen, we have always encouraged our clients to adopt an integrated view when it comes to clinical trials and not to be afraid of agile deployment. To test that the platform that we provide delivers on what we say it offers. Within the space of a month, you'll know if we can do what we said we can do.

to commuting to research sites and dealing with imposed obligations, such as regular medical tests. When the relationships fostered with patients are poor, their adherence to the terms of these trials may dwindle.

- Ineffective trial design. An example of this is the deliberate targeting of older patients (aged 70 or above) with an ECOG performance status of 2 (meaning that they are ambulatory and capable of all selfcare, but unable to carry out any work activities and are up and about more than 50 percent of waking hours) for an indication such as lung cancer. In doing this, many companies will fail to create impactful trials as only a small percentage of the patient population has been targeted. However, pharma companies often default to this type of trial due to pressure from regulators. The FDA, for example, requires that medicines be trialled in special populations – one of which is the geriatric demographic. While they cannot be blamed for this, predictive tools would allow them to realize that this type of trial would most likely fail before it has even taken place.

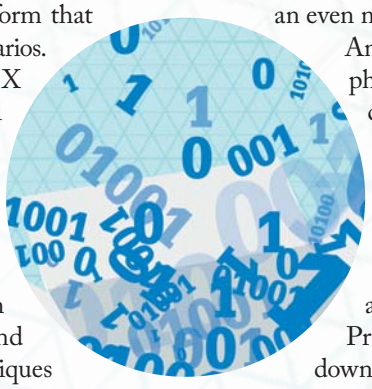
Predicting a data revolution

When clinical trial outcomes fail to translate into benefits for patients, the consequences are dire. Money, time and resources are wasted, and little value is derived. Clinical trials are overdue for an overhaul – AI and machine platforms are the way forward. Some have said that around 80 percent of the data we have today has been created in the last ten years. There has been a data explosion in the last decade. How can individual people cope by manually inputting data, identifying the relevant data and interpreting it?

Predictive analytics is arguably the best tool at any company's disposal when trying to find the needles in big data haystacks and design better trials, with the right sites and the right patients. Predictive analytics provide flexibility and dynamism in ways that more conventional approaches fail to. The rich types of data companies acquire and license cannot be thoroughly analyzed using resources which provide unrefined, basic information about individual trials. Predictive analytical tools are AI-driven platforms that can trawl through large datasets and identify the data most relevant to companies. They can be designed to accommodate ever-growing data sets and have algorithms that allow them to handle data from any source, in any format and allow them to be compared to create recommendations. In our database, for example, we source data from over 70,000 data records. This number grows by around 6,000 records a day. This is an incredible amount of data and with the right tools you can pull effective insight that can help with matters such as finding the right type, location and number of investigator

"There are many companies that have expressed their interest in moving toward more AI-led forms of data analysis."

sites with the right capacity and protocol design in a matter of days, rather than the enormous timelines associated with manual research. Imagine the benefits of being able to use a platform that can analyze "what if" scenarios. What if I was to include X patients in my protocol versus Y patients? Does epidemiology data tell me that there are specific kinds of patients who suffer from this illness?



Of course, even with predictive analytics and other data mining techniques there will never be absolute certainty, but we should be able to use data more effectively and predictably to create value.

A new mindset

At one end of the spectrum, there are many passionate people and companies in the industry who are quick to embrace new technology. There are many companies that have expressed their interest in moving toward more AI-led forms of data analysis, but we find that progress is often hindered because many companies seem unsure of what options are available to them and what it really means for the performance of their valuable trials. But at the other end of the spectrum is the fact that the industry as a whole can be very conservative, preventing companies from expanding their horizons! Just look at how long it has taken the industry to move to electronic data capture.

Though risk-aversion is a problem commonly experienced in pharma, we've found that small to mid-size companies have been quick to trial – and in many cases – adopt these technologies. Some big pharma companies are even building their own platforms, but algorithmically analyzing data in real-time may present problems given the rapid growth of data. By 2020, 1.7 megabytes of data will be generated per person per second. It takes, on average, five years to develop functioning platforms, by which time the data records have already developed to an even more overwhelming size.

Another challenge is that the pharma industry is highly compartmentalized, resulting in the development of functional silos – all of which are key actors in the design of protocol and site selection. Predictive analytics break down the barriers that so often separate professionals whose work lies in the fields of statistics, operational design and medicine. The beauty of these tools is that they work in an integrated manner allowing for study optimization and the prompt activation of sites.

While these two aspects of clinical trial design may seem obvious to clients, this often can't happen using the conventional CRO approach. The use of CROs has historically resulted in poor design, the overuse of underperforming sites for clinical trials and poor recruitment. The majority of trials they design do not optimize centers well or to the same degree that automated platforms can. And while this is not due to ill-intention on their part, their methods simply cannot keep up with the constant floods of data that the industry receives. Many CROs have realized this and are now focusing on data – and it's not uncommon to see large CROs publishing media statements about data acquisitions to show they are serious about data analytics.

But it's not about just acquiring data. Without the algorithms to extract information, data is meaningless. You could have the world's largest database but if you can't filter, compare and contrast that data, there is no value. If you are serious about using your data effectively, don't just buy data; you must invest in the platforms that can mine this data effectively! To address this, we just started to roll out a self-service tool that companies can license to do their own investigator site searching, filtering and selection – utilizing our massive, real time database. We will be adding another integrated module to help companies with protocol planning, enabling them to identify design issues that are the root cause of many recruitment delays.

Predictive analytical tools may seem intimidating and it is common for people to worry that their jobs may be replaced. But predictive analytical tools and data algorithms have not been designed to replace or eliminate roles – they are only helping to redefine them and guide the best path forward for clinical development.

Data is a competitive lever and when taken advantage of, allows companies to reduce costs, compete more aggressively and serve their customers and patients better. It is only when the industry let's go of the momentum of traditional thinking that the greatest successes for clinical trials will be seen.

Gen Li is President and Founder, and Jonathan Peachey is Chief Operations Officer, both at Phesi.

When Standardization Meets Customization

To bring your biologic to market as quickly as possible, streamlined scale up is essential. By combining standardized, single-use platform technologies that can be customized to your particular process requirements, you can unlock crucial efficiency gains.

By Jeremy Rautenbach

Pharmaceutical companies can spend upwards of $2 billion developing a drug (1), but by the time it is ready to be commercialized, more than half of its patent exclusivity period is likely to have elapsed. When you also consider that only a small minority of the Phase I drugs reach the commercial scale (around 14 percent) (2), companies must take full advantage of their marketable drugs to recover their investment costs – this means getting to market as quickly as possible upon receiving Phase III approval.

An important factor in maximizing speed to market is scale up. During Phase II and III studies, companies will be manufacturing small quantities of clinical material and, typically, using equipment that will not support anticipated drug demand during commercialization. Scaling a bioprocess to accommodate larger flow rates and higher output volumes can be a lengthy and sometimes difficult task. Many of the challenges are as a result of making trade-offs between the availability of fundamental technologies (such as instrumentation, pumps and tubing) and optimally operating processing equipment within their designed ranges – this can be a fine (and time consuming) balance.

As well as expertise, a broad technology portfolio including single-use, stainless steel or continuous technologies ensures a choice of manufacturing methods are available to suit. Pall Biotech has such a portfolio of technologies and has further refined its offering by designing standard mAb and gene therapy processing platforms to assist clients with their scale-up requirements. These platforms include all hardware, consumables and interconnecting manifolds, ready-to-go. Development of such platforms has, for example, enabled Pall Biotech to reduce consumables part counts by 30 percent, ultimately translating into reduction in warehousing, increased supply chain flexibility and reduced lead times for clients. However, should these designs not fit the process requirements, they are flexible enough to be configured with relative ease. These hardware systems need to be specified correctly, integrated thoughtfully into the facility, and controlled with the appropriate level of automation to operate efficiently and safely. There are a number of questions that require careful consideration. For example, what equipment is required to support the bioprocess? What are the most optimal process conditions? What is the footprint required to operate efficiently, and what is the associated material and personnel flow within the facility? What is the best method of controlling the equipment, and how will it integrate into the facility's automation architecture?

Biotech Integrated Solutions

Carefully answering these questions and translating process requirements into the correct bioprocessing technologies requires a team of project, design, automation and process engineers, regulatory experts and validation scientists working together from the start. Speed, project management and process expertise are paramount for a successful scale-up to a commercial manufacturing facility, and Pall Biotech has structured its Biotech Integrated Solutions (BIS) team to bring the required expertise to partner with and support clients on their biotech journey.

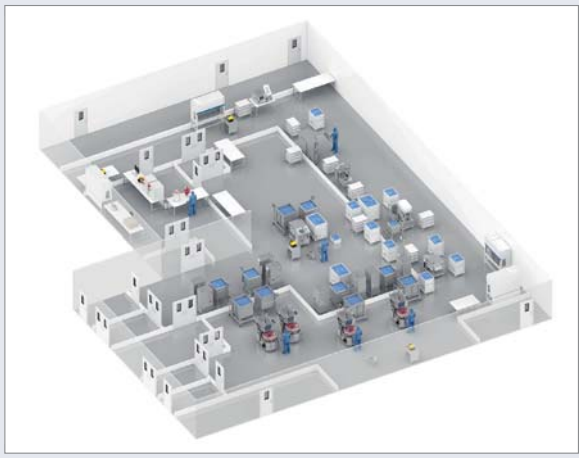


Figure 1: A 3-D representation of Pall Biotech's Gene Therapy platform in the Pall Solution Builder environment.

Knowledge sharing

Before designing a solution, Pall Biotech's team work with the client to fully characterize the process and understand specific needs. A deep dialogue upfront is invaluable and allows the Integrated Solutions team to fully appreciate all the process requirements and translate them into the appropriate technical solution. In our experience, this approach leads to significant savings during project execution because requirements have been well understood and clarified.

To further enhance this dialogue, the team utilizes an internally developed mass balance tool to assist with quantifying expected fluid volumes and product yields to inform system sizing and the equipment list. This tool, in combination with the client's specific mass balance and process description, enables the team to compile a suitable equipment list from Pall's technology portfolio. The design and process engineers have deep technical knowledge of Pall's standard technology

A Servier of Success

Recently, Pall announced that Servier has selected them as an exclusive technology and services provider for their new site in Gidy, France, which will develop and manufacture monoclonal antibodies and recombinant proteins. This supply includes a complete, end-to-end bioprocessing solution from upstream to bulk drug substance.

"We selected Pall Biotech as our single supplier because of their capacity to deliver the complete suite of development and manufacturing equipment, including an automation package, assurance of consumables supply and technical support under a well-defined project execution plan," said Renaud Bessière, Director of the Bio-S Project at Servier in a press release (3).

The facility is part of the Bio-S project at Servier, which is focused on delivering best-in-class support for oncology drug production from R&D to clinical scale. The Bio-S unit will include a development workshop dedicated to monoclonal antibody processes, which will be operational by the end of 2019. The rest of the unit – combining all of the steps necessary to deliver an injectable product to humans – will be operational in 2020.

platforms that allow us to provide guidance on optimal operating ranges, but also identify where equipment may need to be modified to meet individual process requirements.

Solution design

Once the equipment list has been finalized, the Pall Solution Builder platform is used to construct a 3-D model of the client's facility which helps to visualize the intended process flow. The 3-D model helps to confirm the equipment will fit in the facility, provide an appreciation of material and operator flows, and demonstrate the interconnectivity of the equipment and ancillaries. The integration of the equipment into the facility is oftentimes overlooked when generic solutions are proposed, and only discovered during the project execution phase leading to significant rework.

After the equipment and layout have been confirmed, specifying the single-use manifolds, transfer sets and biocontainers can start. Leveraging the existing consumable designs from Pall's mAb and gene therapy platforms and incorporating them into the Solution Builder's 3-D environment, the team will be able to quickly identify any customizations required.

Then, with an approved single-use system, the discussion around automation and control can begin. This conversation is very important because every process and facility is unique. Some manufacturers will require local control of their systems, using PLC or an HMI on each piece of equipment. Others, however, may want to operate their equipment from a centralized node. There are a lot of nuances and it is incumbent on suppliers to build flexible technology platforms that can be modified to suit the company's requirements; for example, larger biopharma companies will have internal automation and control teams. Pall Biotech is aware of these automation nuances and has built flexible technology platforms that can be configured to suit process requirements.

Project execution and delivery

In addition to building and qualifying the equipment, the Integrated Solutions team helps with site acceptance testing, factory acceptance testing, training, maintenance, regulatory guidance and any other service the client requires.

The multifaceted BIS team understand Pall's systems in depth and can identify exactly where the processing limitations are and how they can be balanced to meet the client's needs.

The advantage of choosing a one stop shop over a system integrator as your solution provider lies in the depth of process and technical knowledge that comes from years of designing and qualifying bioprocessing equipment. In short, we know exactly how our equipment works, where it performs optimally and how to configure it to suit the client's process requirements.

Transferring a drug to commercial scale manufacturing at speed is however only one part of the success – the second is ensuring business continuity during the commercial phase. Pall Biotech has a long history of supporting customers during this critical time and has implemented robust supply chain processes assuring customers of supply continuity. Pall Biotech has extensive visibility into its supply chain ensuring and works proactively with its suppliers to ensure adequate risk mitigations are in place – from single-use components supply to irradiation capacity.

When taken forward by Pall, the time it takes to scale up a given process can be dramatically reduced. And the sooner a process is ready for commercial manufacture, the sooner the therapy is on the market treating patients, and the sooner the companies can develop more life-saving medicines.

Jeremy Rautenbach is a Global Product Manager for Integrated Solutions at Pall Biotech.

References

1. *JA DiMasi, HG Grabowski and RW Hansen, "Innovation in the pharmaceutical industry: New estimates of R&D costs", J Health Econ, 47, 20-33 (2016). PMID: 26928437.*
2. *CH Wong, KW Siah and AW Lo, "Estimation of clinical trial success rates and related parameters", Biostatistics, 20, 273-286 (2019). PMID: 29394327.*
3. *Pall, "Pall Corporation chosen as single-source supplier by Servier" (2019). Available at: https://bit.ly/2Nozb9a.*

30 YEARS

CPhI worldwide®

P-mec | InnoPack | iCSE | FDF | BioProduction

5 – 7 November 2019 | Frankfurt, Germany

30 years of uniting the entire Pharma value chain

The world's largest pharmaceutical exhibition, CPhI Worldwide houses six zones representing each stage of the pharmaceutical supply chain – from APIs, machinery, finished formulations and packaging to outsourcing and biopharmaceuticals.

Uniting over 2,500 international exhibitors, CPhI Worldwide is the place to network and source cost effective pharma solutions from all over the world – in just 3 days, under one roof.

REGISTER NOW! Visit gotocphi.com/ddd*

* free registration is available until 15 September. For more information visit cphi.com/Europe

Meet, network & learn

165+
Countries Participating

2,500+
Exhibiting Companies

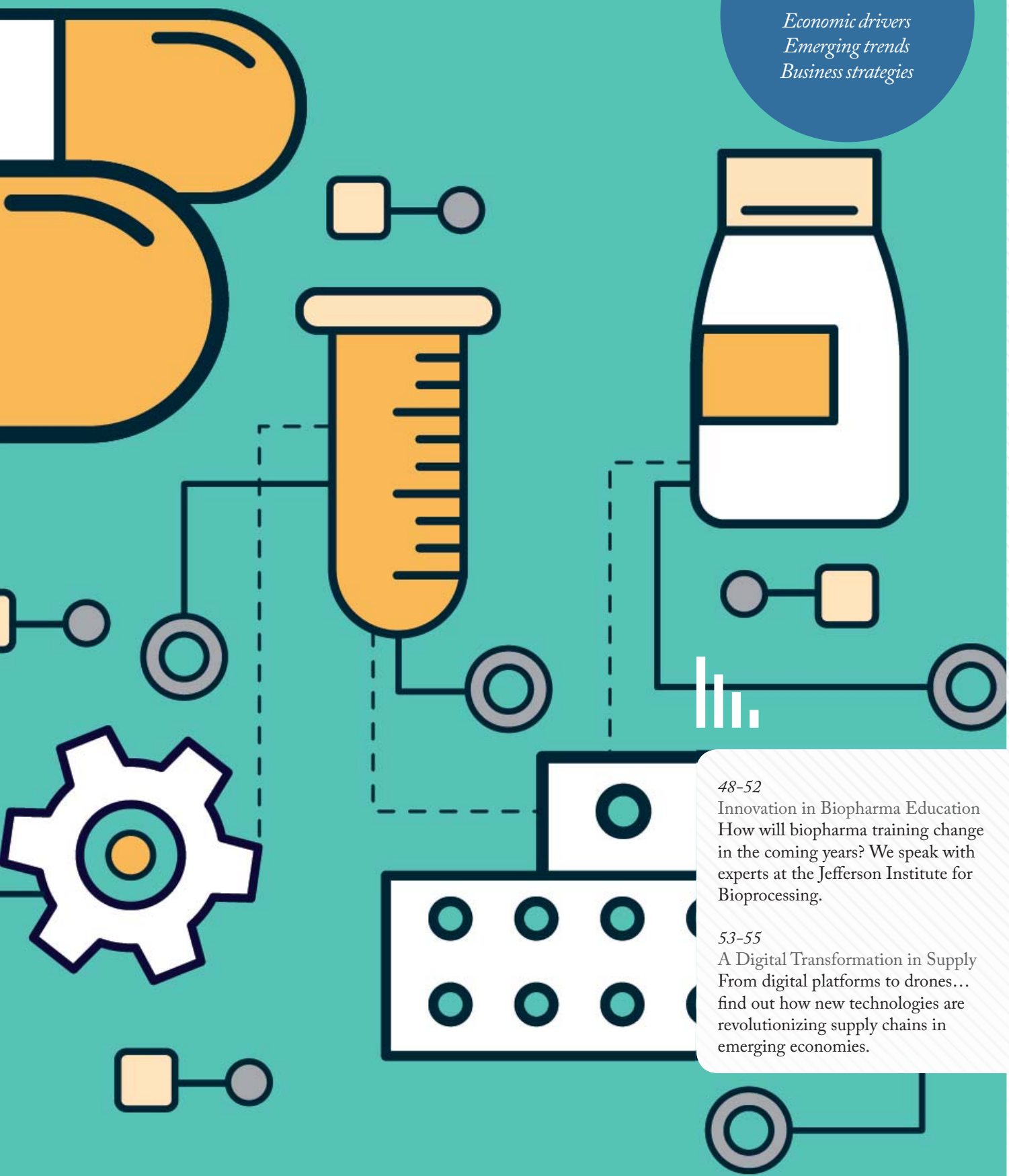
100
Hours of Free On-site Content

> "Everybody here is seriously doing business, looking for business contacts and actively engaging."
>
> **Juan Sarmiento,** Nemera

informa markets

Business

Economic drivers
Emerging trends
Business strategies



Innovation in Biopharma Education

The Jefferson Institute for Bioprocessing is up and running after just two years. How did they do it? What courses are on offer? And how do its leaders see biopharma training developing in the coming years?

By James Strachan

It was Saint Patrick's Day 2016 when J&J's Mary Lynne Bercik was listening to Dominic Carolan, CEO of Ireland's National Institute of Bioprocessing Research and Training (NIBRT) at DCAT in New York City. Carolan was explaining NIBRT's approach to training the biopharmaceutical workforce of the future. NIBRT is a fully functional pilot manufacturing facility dedicated to training and research (see sidebar, "Who or what is NIBRT?"). Bercik, who had graduated from Thomas Jefferson University's business school, wondered whether it might be possible to mirror NIBRT's efforts in the US – the "spark" that ultimately led to the Jefferson Institute for Bioprocessing (JIB), which is now up and running just years two since the collaboration was first announced in 2017.

The JIB delivers NIBRTs curriculum in Philadelphia. And, like NIBRT, it is open to industry professionals who want to take part in workshops and courses, as well as graduate and undergraduate students in bioprocess engineering – one difference is that Jefferson, being a university, can incorporate courses into its degree programs.

Following our coverage of the Jefferson-NIBRT collaboration last year (1), we speak once again to Ron Kander, Executive Dean of Jefferson's Kanbar College of Design, Engineering and Commerce, and to the new Executive Director and Head of the Jefferson Institute for Bioprocessing, Parviz Shamlou, to find out how the institute launched so quickly – and their plans are for the future.

How does the Jefferson Institute for Bioprocessing fit into the new vision for the university?

Kander: Our provost came up with the concept of a "professional Ivy League university." Harvard, Yale, and the other Ivy League universities work synergistically to deliver elite, high quality liberal arts education. We want to create something similar for professional universities. World leaders often come from the Ivy League, but what if we had the same thing for law, business or manufacturing? We want the leaders in those professions to come from an Elite Professional Ivy League, like Jefferson.

We believe we're in a great position to deliver on that concept; the two schools that make up the new Jefferson University (Thomas Jefferson University and Philadelphia University) have always had a strong focus on professional degrees. The Institute part of this larger vision. Our aim is to educate the leaders in international biomanufacturing through hands-on training.

Why is the "hands-on" aspect so important?

Kander: In the American system, there are only three ways to survive as a university right now. The first is size. We're seeing a lot of small schools closing, but the largest universities are not going away. The second factor is endowment. They might not be huge schools, but the Harvards of the world aren't going away either. The third route, the one we have taken, is to focus on value for money – and that means value for employers. Many schools have a hard time demonstrating that college is worth it from a return-on-investment point of view. Students are asking themselves, is it worth paying upwards of $40,000 per year to go to university? There needs to be the promise of a high-quality career at the end – not just a job. By focusing on the kinds of practical skills that employers are increasingly looking for, we're able to place 97 percent of our students in a job or graduate school in their discipline.

And you're also serving a local industry...

Kander: Exactly. Philadelphia is one of the focal points of the biopharmaceutical industry in the US. If you look at biopharmaceutical processing firms and their suppliers, there are hundreds of companies within a two or three hour drive of Philadelphia. Part of our job as a university is regionally supporting the local economy through workforce development structure.

Biopharma is unique in that there's a workforce development deficit across the entire spectrum of roles – from two year associate's degree technicians, to PhDs leading the organization. There are lifelong opportunities for people in this field and it is changing all the time – retraining is key.

Shamlou: Ron is right, training is, and will continue to be, hugely important for the biopharma industry. And not just any old training. If someone is going to work in a biopharmaceutical facility, they will need a set of highly specific, technical skills. Make a mistake in a GMP facility and the consequences could be quite significant for a company. Indeed, companies are reporting that it can takes years to train someone so that they can be trusted.

Our approach is to provide an environment that closely replicates a real GMP facility, where mistakes can be made. So when they do go into a company, they will know exactly what to do. And it isn't just how to operate the equipment – it's quality, cleaning, validation, documentation and other skills that make biopharmaceutical roles so specialized and highly skilled.

Parviz Shamlou

Ron Kander

Kander: At Jefferson, we use the acronym KSA, which means knowledge, skills and attitudes. Applied universities are often good at knowledge and skills, but what makes our facility (along with NIBRT's) so different is that we are also able to develop the attitude component. The industry will tell you that the right attitude is possibly the most important element to successfully working in a GMP environment or as part of a supply chain with a patient at the end of it.

How did you get the Institute up and running so quickly?

Kander: A big factor was that the university was already very industry facing. We were able to reach out to companies and get industry partners onboard from the beginning as part of our advisory board. It was relatively straightforward from there to justify to the university why the Institute would be something of value for the region.

But this outreach and partnering wasn't something we could do by ourselves, so we hired a project management firm and contractors who knew how to do the work. We also had NIBRT as a partner who had been there and done it – they knew where the pitfalls were and their advice was invaluable. Overall, we surrounded ourselves with people who knew how to make this happen!

Shamlou: Another key factor in our time to launch was the focus on next-generation biomanufacturing technologies. If we had opted for a traditional, stainless-steel facility, it would have taken us at least three to four years to get up and running. The facility uses single-use equipment, so nothing is bolted down. This flexibility significantly reduced the time and cost involved. This decision was made based on our conversations with NIBRT – which has both single-use and stainless steel at its facility – and they advised us, as an academic institution, to prioritize single use.

What were the main challenges?

Kander: The facility is an unusual hybrid between an academic institution and a business unit, so the staff working here have to figure things out for the first time, which is a big challenge. We've had to build a team of people that are comfortable with ambiguity – this isn't the sort of place where your job is clearly defined! A major challenge was deciding which parts of an actual manufacturing facility we needed to replicate and which we could

ignore. This created a lot of ambiguity at the construction phase with trade-offs between real-to-life and cost/time.

Shamlou: Exactly. We want to be nimble and responsive to the needs of the industry, while at the same time being conscious of the fact that we're an academic institution at heart. It's an innovation in education itself – one that we think will catch on.

How did NIBRT help?

Kander: The many small snippets of wisdom provided by NIBRT were significant over the course of the whole project! One example was that NIBRT put their upstream and downstream processing unit in the same room, which from a manufacturing point of view, made perfect sense – that's how real facilities are set up. They quickly realized that if you have two groups of students in that room, however, you end up with everyone yelling over each other. They had to stop that. We put the upstream in one room and downstream in another. It might not replicate a real facility exactly but it's worth it to maximize our space.

Shamlou: In addition to practical tips, collaborating with NIBRT has been invaluable for our credibility. Any new facility needs time to grow and be accepted by the community. NIBRT has been around for over a decade and is accepted as the gold-standard in this space. Through our partnership with NIBRT, people already know that our courses will be of high quality and properly regulated and audited, which should accelerate the credibility-building process for us.

Can you give us an overview of JIB's courses?

Shamlou: We will provide the same courses as NIBRT, as well as some of our own. We also want to harmonize the way we deliver those courses, so that a company with people in America and Europe could send their staff to Jefferson or NIBRT and they'd both receive the same experience. We've been working closely with NIBRT to make this harmonization a reality.

In short, we're offering courses on everything from API presentation, storage and stability, cell line, inoculation, cell expansion to viral safety, chromatography, buffer exchange concentration operations, nano filtration, freezing and thawing of API – and many more. We also have courses that integrate these individual operations to give an end-to-end overview of the process.

Kander: There's really two markets for training: people who are going to be operators on a given unit and those who will never work in bioprocessing – people in sales, marketing, business and so on – who still need a good understanding of the overall process so that they know what they're talking about when dealing with customers or suppliers. We offer both kinds of courses.

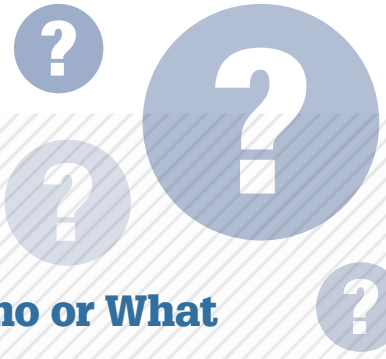
Anyone can register for our "open enrollment courses," which run for two or three days. But we also have "customized courses," where a company might send 10 to 12 employees and we will deliver training specific to their needs. The company might also choose to bring their own expert to deliver the course at our facility.

In fact, Parviz has had conversations with companies who may want to bring specialized equipment into Jefferson to train their people on how it interfaces with other equipment.

Are the courses also integrated into your degree programs?

Kander: Yes! One big difference between ourselves and NIBRT is that, because we're a university, we can turn these courses into accredited elements of a degree program – undergraduate and postgraduate. We're bringing in our first students this academic year.

We're working with three different colleges, and four or five degree programs within those. So you might be a biochemistry, biotechnology or engineering student, and you would take courses at the institute as part of your



Who or What is NIBRT?

NIBRT is a fully functional pilot manufacturing facility dedicated to training and research, based in Dublin, Ireland. Everything is done to GMP standard, but people can make mistakes without costing a company any lost revenue. The biopharma industry sends staff to NIBRT for customized training programs, and students from higher education institutes visit for a hands-on manufacturing experience. The institute opened its doors in June 2011 and trains approximately 4,000 people each year (2).

In 2016, NIBRT received additional grant funding to expand its R&D activities to match it's training program (3). Its main focus areas are downstream processing, engineering and manufacturing technology for next generation therapeutic platforms.

For example, NIBRT recently announced a collaboration with Allergan to address challenges in Adeno-Associated virus (AAV) production (4). "Given the potential for gene therapy to transform patients' lives, this collaboration will help progress both the analytics and process which are currently the main challenges in the production of high quality AAV medicines," said Crawford Brown, SVP Biologics & Small Molecule (API) at Allergan.

degree program. We're also looking at a post-graduate degree program where a student would do all 30 credits here. And we are open to partnering with other universities in the region.

What made you such a good fit for NIBRT?

Kander: NIBRT had previously approached universities in North America and couldn't get traction because of how slowly traditional academic institutions tend to move. They needed a university that could keep pace with a rapidly changing industry. Jefferson is an industry-facing university and understands the need to be able to move quickly.

Shamlou: We both understand that the industry is changing rapidly. We're looking at the rise of cell and gene therapies, advanced vaccines overtaking proteins and monoclonal antibodies. To do what NIBRT does you have to be able to respond quickly.

What are your plans for advanced therapies?

Shamlou: Right now, we have 25,000 square feet of empty space that we're ready to expand into. If we get approval from leadership – and provided we find the right partners – our vision is to grow out training programs into cell therapy, gene therapy and other up-and-coming areas. Watch this space.

How do you see biopharma training developing in North America?

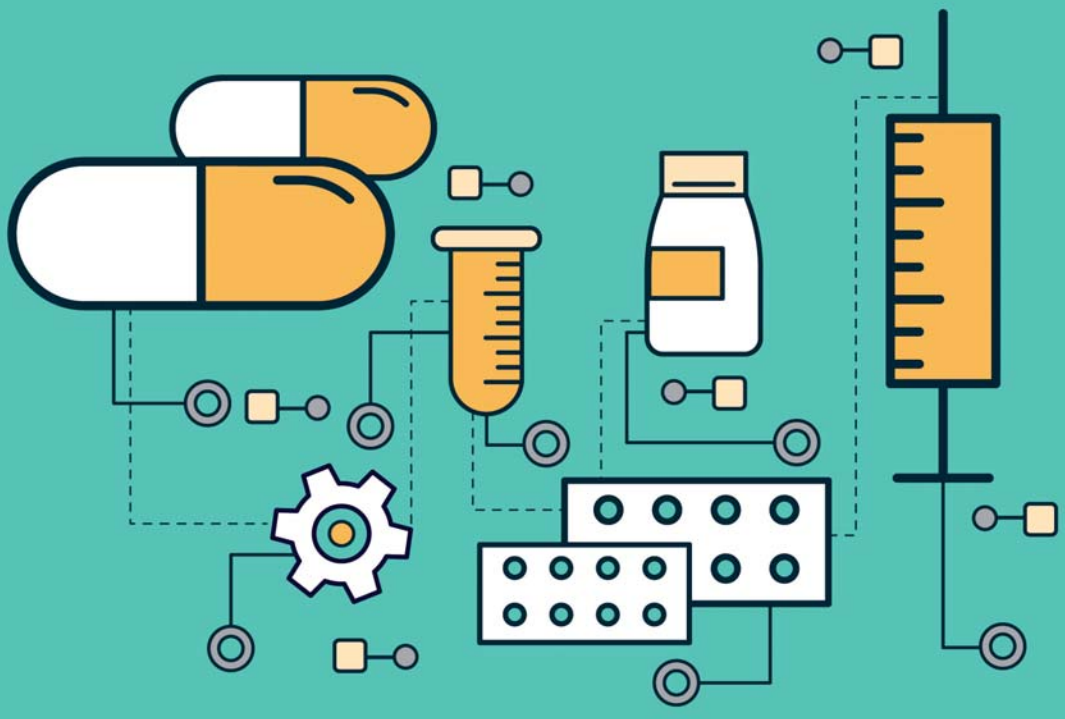
Kander: Through our agreement with NIBRT, we have exclusive North American rights to their curriculum. So any other facility in North America that tries to implement the same courses would have to come about via partnership. Indeed, we might see satellite organizations popping up elsewhere in North America. I could eventually see NIBRT building a global network with facilities in the Pacific Rim, Africa or elsewhere in Europe, all teaching the same curriculum.

We're also trying to build a consortium, called NIIMBLE (National Institute for Innovation in Manufacturing Biologics), which is currently made up of 30 or 40 universities and companies, to standardize training. We strongly believe the pie is big enough for everyone and we're taking a leadership position in helping develop training capabilities across North America.

Shamlou: We see great potential in partnership, as opposed to competition. Jobs in this sector are growing rapidly both nationally in the US and globally, and can't be filled because there aren't the training facilities available. What we need, as Ron said, is a network of facilities worldwide, all meeting the same high standards.

References

1. *Kathy Gallagher and Ron Kander, "Training the Workforce of the Future" (2018). https://bit.ly/30m3Qr7.*
2. *Barry Heavey, "A Tale of Irish Biopharma" (2016). https://bit.ly/2HcVJFZ.*
3. *Killian O'Driscoll, "Sustaining the Biopharma Boom" (2016). https://bit.ly/2TQHBHq.*
4. *NIBRT, "Allergan and NIBRT announce gene therapy research collaboration" (2019). https://bit.ly/2KDr2vu.*



A Digital Transformation in Supply

How advanced solutions can boost the quality of supply chains in emerging economies.

By Maryam Mahdi

Foreign aid is – and will likely remain – a topic for debate in countries on the giving end. Some believe the money should be spent on issues closer to home and others have suggested that foreign aid does nothing for inequality. But such conversations are not limited to one side of the equation – those on the receiving end also hold strong opinions about foreign donations and their capacity to facilitate change.

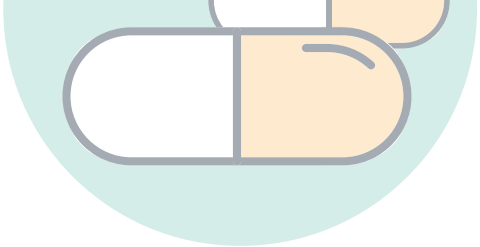
Although many emerging economies rely upon funding support to purchase medicines, improve healthcare infrastructure, and train staff, they are also keen to shake off the idea that they are unable to do it alone; after all, 70 percent of the world's population lives in emerging economies (1) and they, like the citizens of every other country, have a desire to see their healthcare and pharmaceutical industries improve.

For these countries to become independent of the aid provided to them, they must tackle a number of hurdles. Access to medicine is dependent on a functioning, efficient supply chain – a significant and proven challenge for low-income countries. In 36 low-middle income countries in WHO regions (Africa, Americas, Eastern Mediterranean, Europe, Southeast Asia, and Western Pacific), the average availability of medicines is a low as 29.4 percent despite medicines accounting for up to 60 percent of health spending in these areas (2). Further to this, patients are often left to foot the bill of medical care, with up to 90 percent of the population in low income countries making out-of-pocket payments for much needed treatments (2). As the governments of countries with the greatest disease burden struggle to find the talent and resources to deal with the end-to-end demands of a well-greased pharmaceutical supply chain, patients feel the significant consequences. Digital technologies are, however, emerging as solutions to address the structural demands of the industry.

Maeve Magner is an industry-renowned global health supply chain and market access advisor, whose clients include the Bill & Melinda Gates Foundation and multinational pharmaceutical companies. At the recent FutureLink Barcelona event, she told The Medicine Maker how digital platforms can transform the supply chains of developing nations.

What problems arise as a country becomes wealthier?

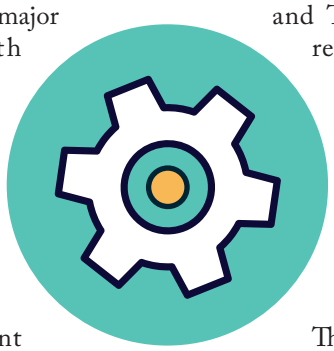
Though the number of middle-income countries is rapidly growing, it is important to remember that these nations still contribute to around 70



percent of the global disease burden. It is essential that they are able to navigate and manage their healthcare and pharmaceutical sectors.

As countries transition away from their low-income status, their pharmaceutical and healthcare industries often remain unchanged, which is to say, small and fragmented due to attitudes toward drug purchasing (often the governments of these countries fail to buy drugs for the entire nation; rather, clinics place small, separate orders). Economic growth also results in the swift withdrawal of foreign aid, leaving them to deal with higher drug prices (as they are no longer able to receive cheaper drugs with the help of international organizations) and the challenges of restructuring their healthcare and pharmaceutical industries. Though the move may seem like donors pulling the carpet out from under these countries' feet, the intention is to inspire them to fund and sustain their own health programs, helping to eradicate the need for foreign assistance altogether. But when nations are unable to negotiate deals for cheaper medicines, some of the world's poorest and most vulnerable patients are left without regular access to much-needed therapies as expired products, which, of course, are of no use to anyone! Essentially, the issue boils down to a need for better forecasting, procurement and distribution so that stockouts cannot happen.

These problems have a major impact on the smooth running of supply chains, but fortunately there are initiatives aimed at building awareness. People Who Deliver, is one such example. Represented by governments, donors, non-government organizations, academic institutions and private investors, the organization partners with other global agencies to help develop the professional expertise of supply chain personnel. The organization also works with governments to help them develop strategies to help encourage young people to consider careers in the field and to create a demand for these important services within the countries they support.



With the help of these types of organizations, countries are learning to budget and prevent wastage from happening; creating more efficiency in their supply chains for years to come. By eliminating these inefficiencies, more funds can be effectively diverted to address the requirements of a well-functioning supply chain.

What problems can affect the supply chains of emerging economies?

When countries lack personnel with expertise in supply chain management, it has a knock-on effect on how well people understand the end-to-end demands; the need for robust training is obvious. Employees need to understand how to use the tools that large pharmaceutical companies use to discern how much they should be paying for drugs. But the problem persists far beyond the drug purchasing process.

It is not an uncommon occurrence to see essential medicines stored in the same warehouses that house food products from United Nations agencies, as well

How do digital platforms help?

Digital platforms for supply chain management are becoming more commonplace. Some western countries can be reluctant to adopt new technology (often because of challenges in integrating it with existing models and supply chain processes), but in many emerging economies there is a hunger to adopt digital technologies as they are the fastest method for implementing real change. For example, M-Pesa, a mobile money transfer service, was was first set up in 2007. The service initially allowed for the safe transfer of cash for East African (Kenyan and Tanzanian) citizens. Its reach has now expanded allowing customers from Afghanistan, South Africa, India, Romania and Albania to pay bills, set up savings accounts, apply for loans and insurance and purchase airtime. Though M-Pesa facilitates financial transactions, there is definitely scope for similar technologies to be developed and enhanced to help support the pharmaceutical industry and its supply chains.

East African nations are also proving that they are ahead of the curve with other technological innovations. For example, drone technologies are being used in Kenya and Tanzania to transport both blood and medical products to hospitals and clinics.

Tanzania's Civil Authority is also one of the world's first to develop strategies for managing the air traffic caused by drones and aims to make the country drone-friendly while protecting its airspaces. Zanzibar, a semi-autonomous region of Tanzania, has the highest density of young drone pilots anywhere in the world. Imagine the possibilities if this expertise could be exploited to effect change in pharmaceutical logistics – not just in East Africa but globally.

What else can advanced nations learn from low-middle income countries?

Advanced economies really do have the opportunity to learn from the innovative mindset that is whole-heartedly embraced by low-middle countries! Unconventional players enter the pharmaceutical market, shaking up

the way it operates. Companies who started in the telecoms and technology sectors like Google and Apple now have a growing presence in the industry and therefore it is important the traditional pharma players don't lose their relevance in the eyes of patients. Huge nontraditional companies are proving that they are willing to engage with patients in a very direct way, changing the way that patients interact with the industry. The recent partnership between Amazon, Berkshire Hathaway and JP Morgan is intended to form an independent healthcare company for their employees and is another example of industry outsiders transforming the pharma landscape. Well-known pharmaceutical companies will have to become more flexible and agile to keep up with the changing tide.

Some pharmaceutical companies are going out of their way to invest in novel technologies, such as blockchain, which is making a buzz in the supply chain world. But sometimes it feels as if these efforts are box checking exercises to demonstrate innovation, rather than a true belief that they will result in real change. Despite all of the communication technologies available today, many companies still haven't taken the time to create meaningful points of communication with patients and understand their concerns. Patient-centricity has to become more than a buzzword for traditional pharma to maintain its relevance in a rapidly changing sector.

Are the upfront costs of new supply chain technologies a barrier to adoption?

Low-middle countries have been the target of many pilot projects for digital models that aim to improve the access that patients have to medicines. But understanding how expensive these models will be to roll out in real life is necessary if they are to bring long-lasting benefits to healthcare systems.

If these models are able to demonstrate their inherent ability to address patient needs in a simplistic and interoperable manner; attract engaged stakeholders and function in a policy environment that prompts the use of such technology, then there is no reason why low-middle income countries should be priced out of adopting digital technologies. Many low-middle countries are already adopting digital platforms, such as those to deter counterfeit medicines, so further supply chain digitalization is not out of the question. In fact, I am optimistic in the ability of these countries to spark meaningful and lasting change through digital platforms on a global scale. But we must ensure they have the support needed to allow them to reach their full potential.

The topic of digital supply chain platforms will be further explored at FutureLink Nashville, October 2–4.

References

1. *T Ottersen et al., "The challenge of middle-income countries to development assistance for health: recipients, funders, both or neither?" Health Economics, Policy and Law, 12, 265-284 (2017).*
2. *A Cameron et al., "Medicine prices, availability, and affordability in 36 developing and middle-income countries: a secondary analysis". Lancet, 17;373, 240-249 (2009).*

Choose Your Playing Field

So you want to build a new facility for advanced therapy manufacture? Before you start building, there is one essential element that you need to get right: site selection.

By Grace Linton and Charles Heffernan

At first glance, the needs of an advanced therapy medicinal product (ATMP) facility may seem to be no different to those of a traditional bioprocessing facility – and indeed the clean rooms, testing and admin facilities will be very similar. Once you move into the commercial manufacture of ATMPs, however, more specific requirements will become apparent, particularly the "scale-out" rather than "scale-up" concept, gowning and segregation requirements, as well as community perception of the facility.

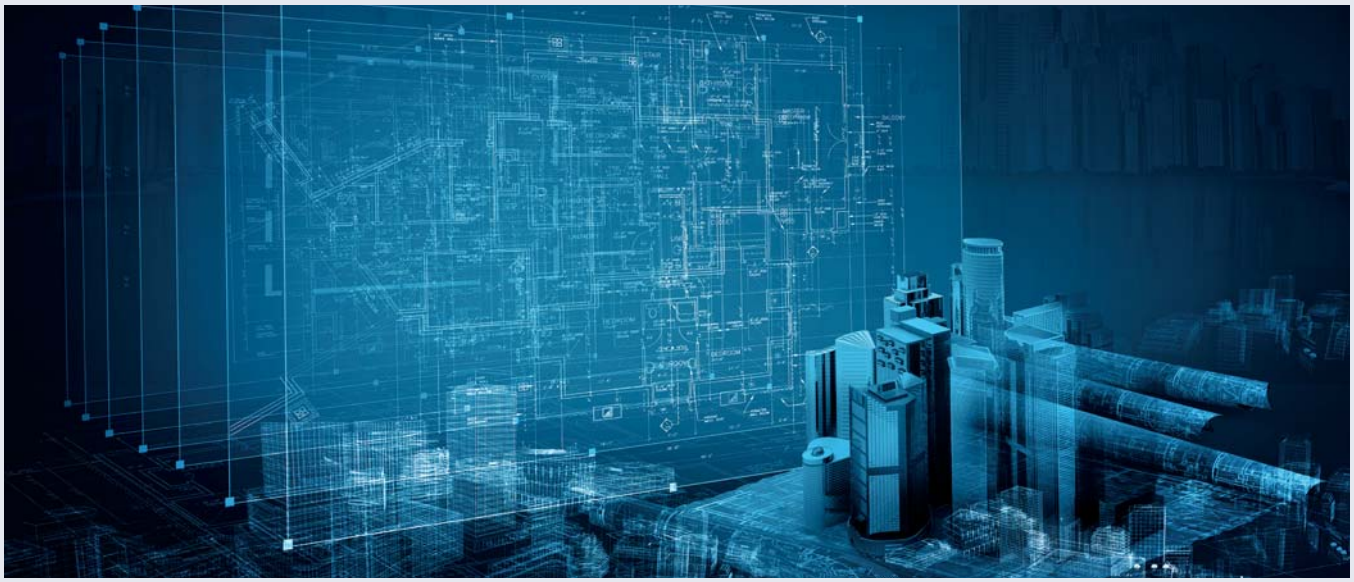
Building a facility that is fit for purpose begins with site selection. Your first choice is whether to build on a greenfield site – an undeveloped site with no pre-existing buildings – or fitout an existing shell building. It is common for companies to have surplus pharmaceutical manufacturing sites or warehouses that they wish to make use of, but in our experience, it can be difficult to optimize existing buildings for ATMP manufacture. With ATMPs, you need to consider expandability when creating the facility – how are you going to expand to accommodate future capacity as the business grows? This is particularly relevant for many autologous ATMP processes, since these can be manual and labor intensive, requiring additional space for expansion of capacity. These same limitations can apply to utility systems. If your space is constrained from the start by an existing building, then it can be tricky to truly optimize the facility.

One cell therapy client we worked with selected what seemed to be an appropriate site in an urban city block in New York, but the project came undone once they considered their liquid nitrogen distribution strategy. There was no space for bulk tank storage (space is always at a premium in big cities), so they had to consider the use of portable cylinders, but that meant there would be an enormous quantity of cylinders to move throughout the building. When moving liquid nitrogen in enclosed spaces, such as an elevator, you cannot have an operator in the same space because of asphyxiation hazards. You need to set up a shipping and receiving dock for the cylinders, and you need a way of getting them into the elevator and transporting them without a person. Additionally, you need to ensure everything is logged. Ultimately, it would have commandeered one or two elevators during shifts. And logistically that wasn't going to work, so the site choice was abandoned. The client moved to another site where there was a shell of an existing warehouse that could be better designed to suit their needs. If you are opting for an interior fitout option, then try to ensure that the space selected allows for flexibility.

Making the location work

Local incentives from governments and municipalities will almost certainly play a large role in the choice of location. Many areas offer local funding or workforce training to attract business investment, which will ultimately affect the overall cost of developing a new facility. The help available can also impact the time it takes to get the facility up and running – perhaps by accelerating the granting of necessary permits, for example. For ATMPs, however, the most important aspect regarding location often involves transportation logistics. Autologous ATMP therapies involve getting cells from and to patients or treatment centers – often very quickly. Some companies consider a chain of regional distribution centers, but being located close to a major airport or transport hub is usually desirable. If your site is to be located in a remote region, you can still set up your own transport links using private couriers – although few companies choose this option. It can also be necessary to rule out certain areas because of their weather patterns. If roads or airports are frequently closed because of storms, then it could seriously affect the therapy reaching the patient – and ATMPs really can be a patient's last chance at life so delayed treatment could be fatal.

You also need to consider access to a skilled workforce. Given the fact that there are few automated solutions for manufacturing ATMPs, processes are manual and require attentive and highly trained workers who can perform the process in line with cGMP. An obvious solution is to locate your factory in a populated area with other ATMP companies, as well as prestigious universities. This makes the hiring process easier – and you can also partner with universities and local



schools to raise awareness among younger talent – but it can also result in high staff turnover because of the competition. If you are planning to locate your facility in a competitive area, it pays to think about what you can do to retain staff. Companies like Google have gone to extreme lengths to make their facilities attractive to staff! Few pharma companies are willing to go that far but considering lounge space and amenities, such as a creche or a fitness center, can be hugely beneficial in attracting and retaining staff. If this isn't an option – many ATMP companies are small so may not have the capital available for optional extras for staff – consider alternative options that will make the company attractive, such as partnerships with local facilities and cafes. You can also partner with nearby companies to share meeting spaces.

It is also worth considering the fact that in populated areas, space can be at a premium, which brings us back to the need for potential expansion during the lifetime of the ATMP therapy. In a less populated area, while it may be initially harder to staff employees, there is the opportunity to train a stable, dedicated workforce. Sites may be larger and less expensive too, but this may be offset against the transportation logistics and other factors including access to vendors, and disposal of medical waste, which can be more expensive.

In many cases, we find that companies lean towards populated areas. But the final decision may also be influenced by upper management – who may simply want to choose a location that is nice to live in or that is close to the company's roots.

Flexibility for the future

From the very start of a project, you need to go through your process every step of the way. Where is your incoming material coming from? How frequently will it come? What space does it require? Where will it be stored? How do the materials move about the facility? What space do you need for cleanrooms? And then how is the therapy transported back out to the patient? You need a good picture of the physical space involved in all aspects of the manufacturing process. We recommend using modelling to understand what will happen in each of the key spaces and to determine the requirements. In our experience, the hardest part for clients is making key, pivotal decisions early in the project and keeping to those decisions throughout the project lifecycle. If you cannot decide what your needs are then it will be difficult to choose the right site and to optimize the facility design. As one consideration, if you don't know how many employees you'll have, then it will be difficult to plan for parking, employee facilities, gowning, and how many people you'll actually have in a cleanroom and how this affects the facility layout. Cleanrooms and quality laboratories are often the main considerations and it's very easy to overlook everything else that is required for a facility.

We've outlined only a brief selection of factors that may influence site selection – there is far more to consider. But for ATMPs, the biggest advice we can offer is to choose a site that is flexible – this could be a greenfield site or a flexible shell building for interior fitout. The era of ATMPs is only just beginning; technology is changing fast and a lot of lessons are being learned as more therapies reach the market. Your facility needs to be flexible to adapt to new trends and to be future proofed for next generation therapies.

Grace Linton, AIA, LEEP AP BD+C, is a Process Architect and Charles Heffernan is Director of Process Engineering, both at CRB.

Putting the Brakes on Aging

Sitting Down With… Joan Mannick, Co-Founder and Chief Medical Officer at resTORbio, Massachusetts, USA.

Who has inspired and mentored you over the course of your career?

My father was a great source of inspiration. Like many other of my family members, he worked in academic medicine and held the belief that a person should always try to make positive contributions to society. From a young age, I was intrigued by tropical infectious diseases and assumed that I would follow in my father's footsteps and have a career in academic medicine. I gained my medical degree from Harvard Medical School and served as a faculty member specializing in infectious diseases at the institution for eight years. Though the experience was incredibly rewarding, juggling various aspects of life became challenging. I was a mother trying to best meet the needs of my children; an academic dedicated to running a lab; and a doctor trying to see patients.

Around the age of 50, I expressed my concerns to my father, who encouraged me to try something new. I knew that I wanted to bridge the gap between basic and clinical science because I was very familiar with them both, and I soon found myself as a Medical Director at Genzyme. I felt comfortable in the role because I knew I could work closely on the translation of basic science to patients.

The transition from academia to industry was one of the best moves I've made in my life, and I would implore anyone at any stage of life to evaluate whether their career is right for them. Be brave and take the leap because, more times than not, you'll find something that you truly love and are passionate about!

After three years at Genzyme, I moved to Novartis where I had the good fortune to work under Lloyd Klickstein. He was the type of leader who wanted to make his whole team shine. He would give us credit for the work we did and supported us when our work entered new (and often unknown) territory. After working with Lloyd, I aspired to be such a good mentor. The people you work with are oftentimes more important than the actual work, so good mentorship is essential.

What appealed to you about working for Novartis?

I began working at Novartis in 2014 in its New Indications Discovery Unit. The unit was started to address areas of medicine that didn't fit into the traditional categories used by most big pharma companies. Instead of focusing on more mainstream indications like cardiovascular disease or oncology, we tackled areas that typically fell between the cracks of drug discovery and development. It was a great period of my career because Novartis encouraged its staff to think outside the box in an effort to transform the practice of medicine – and that was exciting!

I was given free reign and started a drug development program focusing on the process of aging; after all, the elderly are the fastest growing population around the globe. I felt that my colleagues and I had the opportunity to make an impact on the lives of a significant number of people. I believe that by targeting the biological mechanisms controlling aging, we can challenge the notion that a person should expect to experience illness as they get older.

How did you end up at resTORbio?

My team and I completed two successful trials at Novartis, and the results suggested that targeting the biology of aging improves immune function and thereby decreases infection rates in the elderly. Although the research was illuminating, it didn't fit into any of Novartis' late-stage development programs – in part because one disease area couldn't encompass all of the disease implications caused by aging. I worked with my cofounder, Chen Schor, to license the program – and eventually resTORbio was born.

What are the most important lessons you have learned since starting the company?

I've learned that regulators are open to the development of drugs targeting the biology of aging and that they recognize that we have the same goal: to help patients by finding medicines with clinical benefits. Scientists pursuing their own start-ups will inevitably have to work with regulatory bodies, so my advice is to be open to their suggestions and criticism because their intention is to ensure that safe and effective products make it to market.

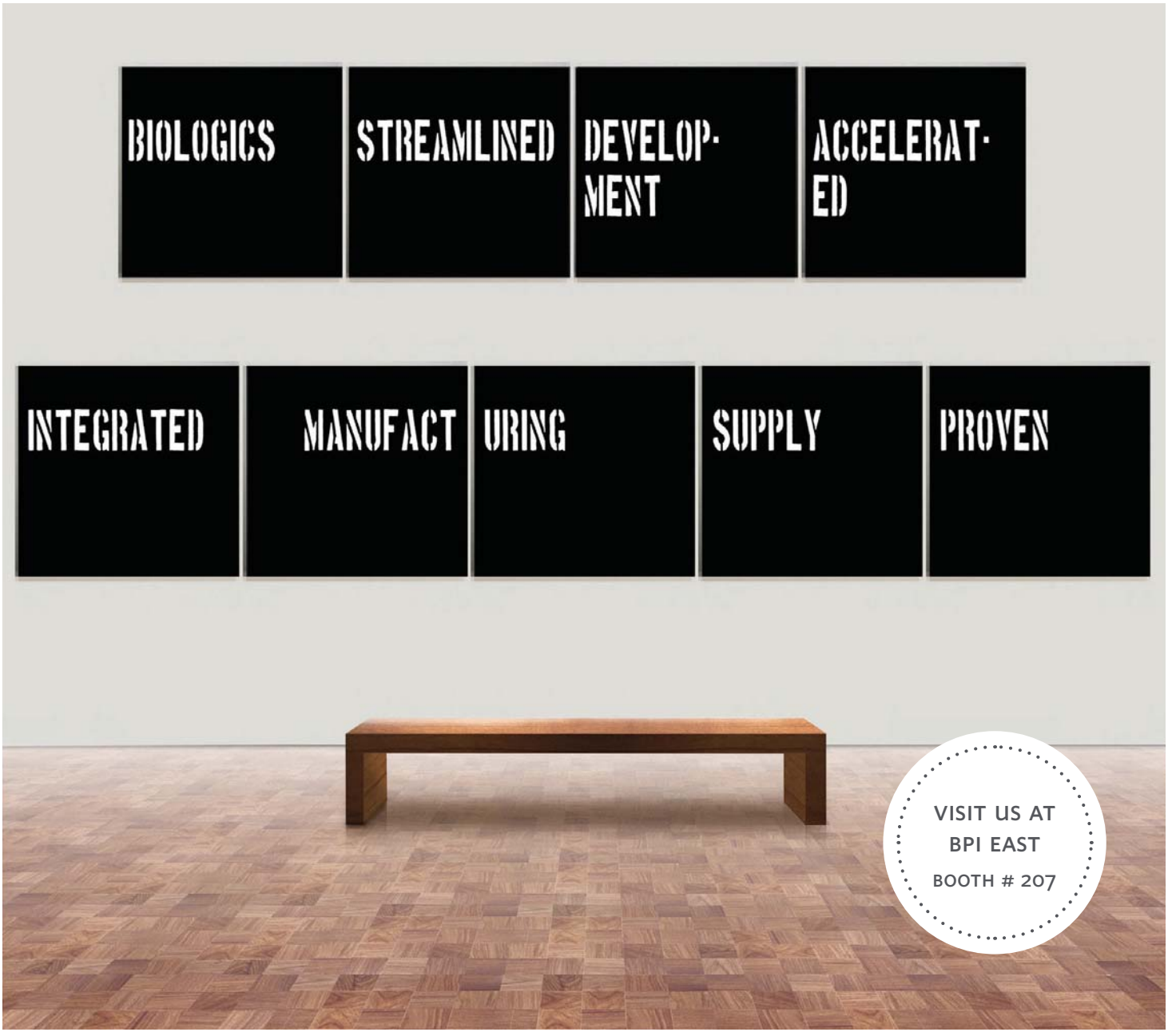
In addition to working alongside regulators, it is also important to educate investors on the biology of aging and the opportunity it provides to help patients and the healthcare system. Rigorous scientific data has been generated by highly respected investigators around the globe on the identification of biochemical pathways that regulate the process of aging. The field has advanced to the point that we have been able to move this science to humans and evaluate the efficacy of compounds that target the biology of aging to treat aging-related diseases in randomized, double-blind, placebo-controlled trials.

What are the company's plans for 2019 and beyond?

Finding drug targets for the biology of aging is no longer decades away! Our first of two planned Phase III clinical trials is underway, and we expect topline data from both trials in 2020.

How would you change the industry for the better?

Currently, not much attention is being paid to developing drugs for diseases that cause huge health burdens for millions of elderly people, such as neurodegenerative diseases, sarcopenia, viral respiratory tract infections, and certain types of heart failure. Therefore, we must spend more time and effort on developing new medicines that will help large populations suffering from these common diseases for which there are no current treatments.



CREATING BIOLOGIC TREATMENTS IS SCIENCE. ORCHESTRATING FASTER DEVELOPMENT IS ART.

Introducing our latest masterpiece, OneBio℠ Suite, which integrates development through complete clinical and commercial supply to simplify, accelerate and de-risk your biologic development.

With our deepest expertise and advanced technologies, we help you deliver better biologic therapies to patients, faster. **Catalent, where science meets art.**

Catalent
BIOLOGICS

us + 1 888 SOLUTION (765-8846) **EU** 00800 8855 6178 catalent.com/onebio