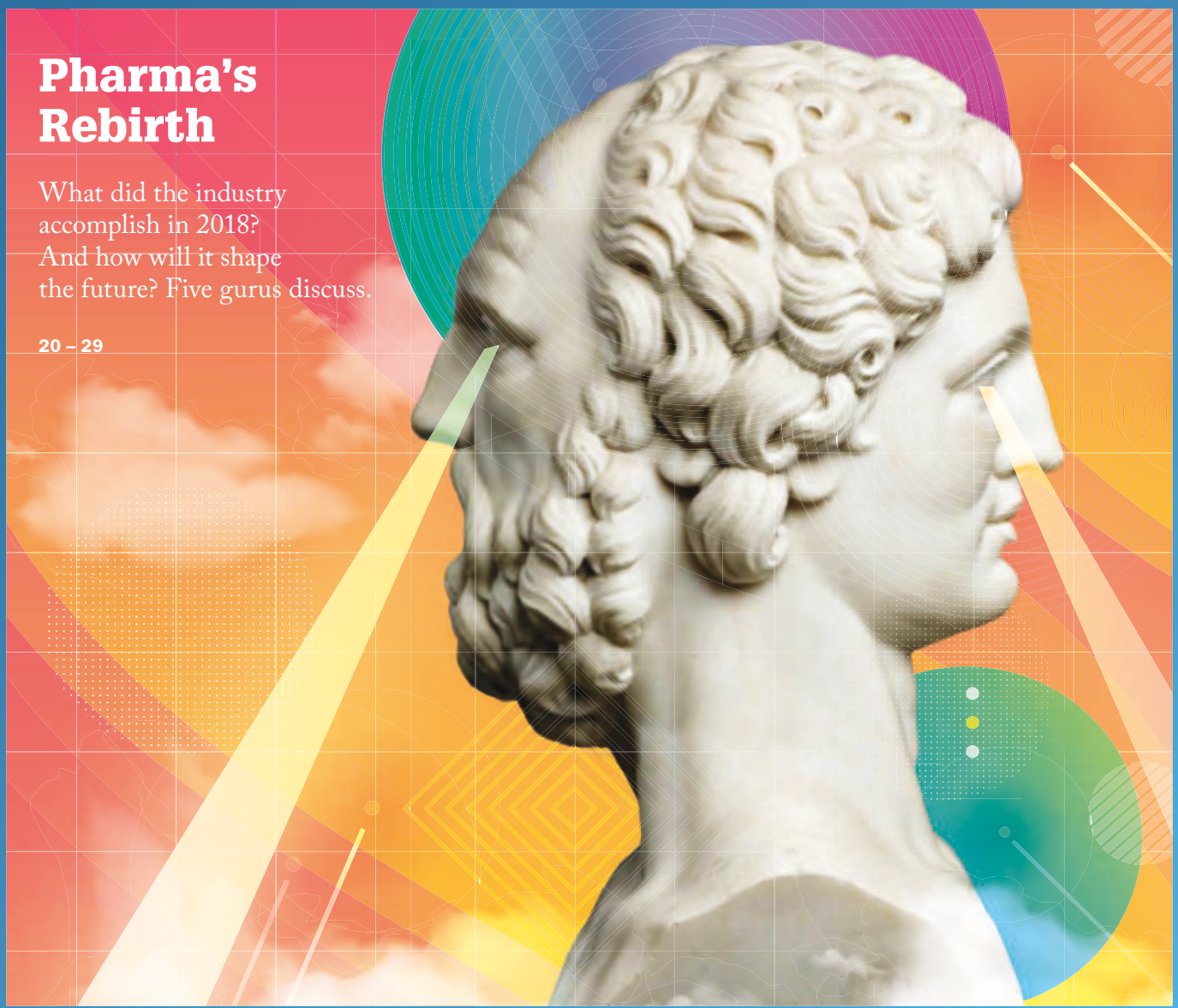
JANUARY 2019 # 49

the Medicine Maker™



Pharma's Rebirth

What did the industry accomplish in 2018? And how will it shape the future? Five gurus discuss.

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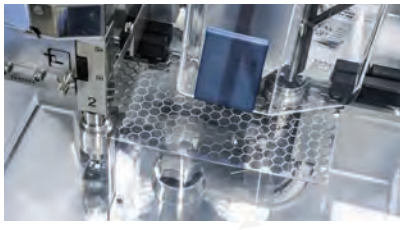

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Online this Month

You can read more about the 16 winners at www.themedicinemaker.com.

- Co-creation of COC containers
- Colorista
- Cyto-Mine
- Endozyme II Go
- Eshmuno CP-FT
- LinearTwinScan
- Lyo-Check
- Master Data Collaboration Tool
- Microcell Vial Filler
- NovaTrack
- Orbitrap ID-X Tribrid Mass Spectrometer System
- Q Exactive UHMR Hybrid Quadrupole-Orbitrap Mass Spectrometer
- Smart Blister Pack
- syriQ BioPure
- UBERcellFLEX
- Zydia Ultra Coating Technology

Who's the Best?

Vote for the grand winner of The Medicine Maker 2018 Innovation Awards!

Our December 2018 issue saw the publication of The Medicine Maker annual Innovation Awards, which showcased the top 16 drug development technologies launched during 2018. Our 16 winners beautifully demonstrate the diverse technologies and capabilities required for developing new drugs, but which winner is truly the most innovative? It's up to you to decide.

Go to http://tmm.txp.to/2019/innovationvote to quickly vote for your favorite technology. We'll publish the development story behind the most popular technology in a 2019 issue of The Medicine Maker. Voting will close on February 28, 2019.

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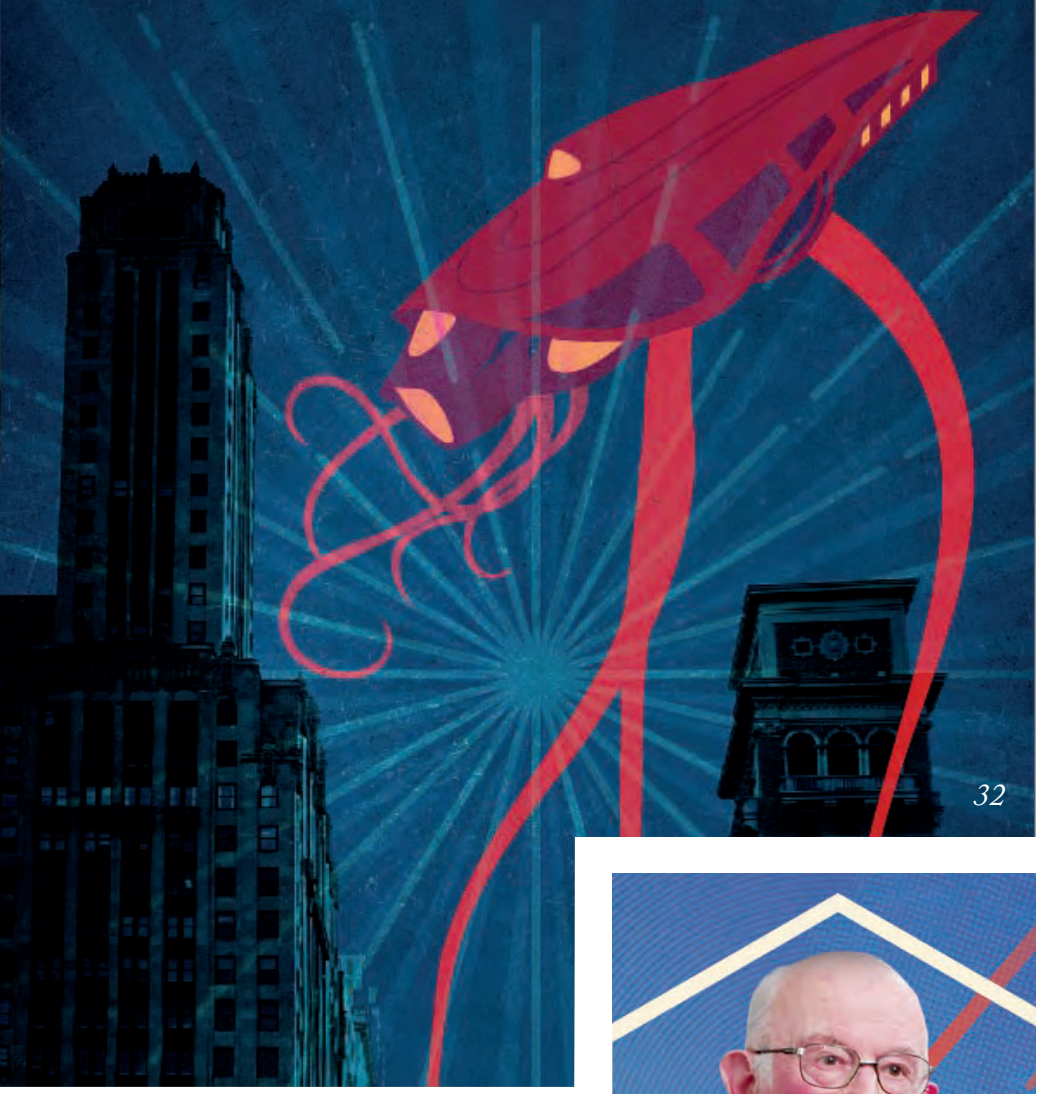
Janus, the Roman god of beginnings, endings and transitions.



Business

Reports

Sitting Down With

the **Medicine Maker**

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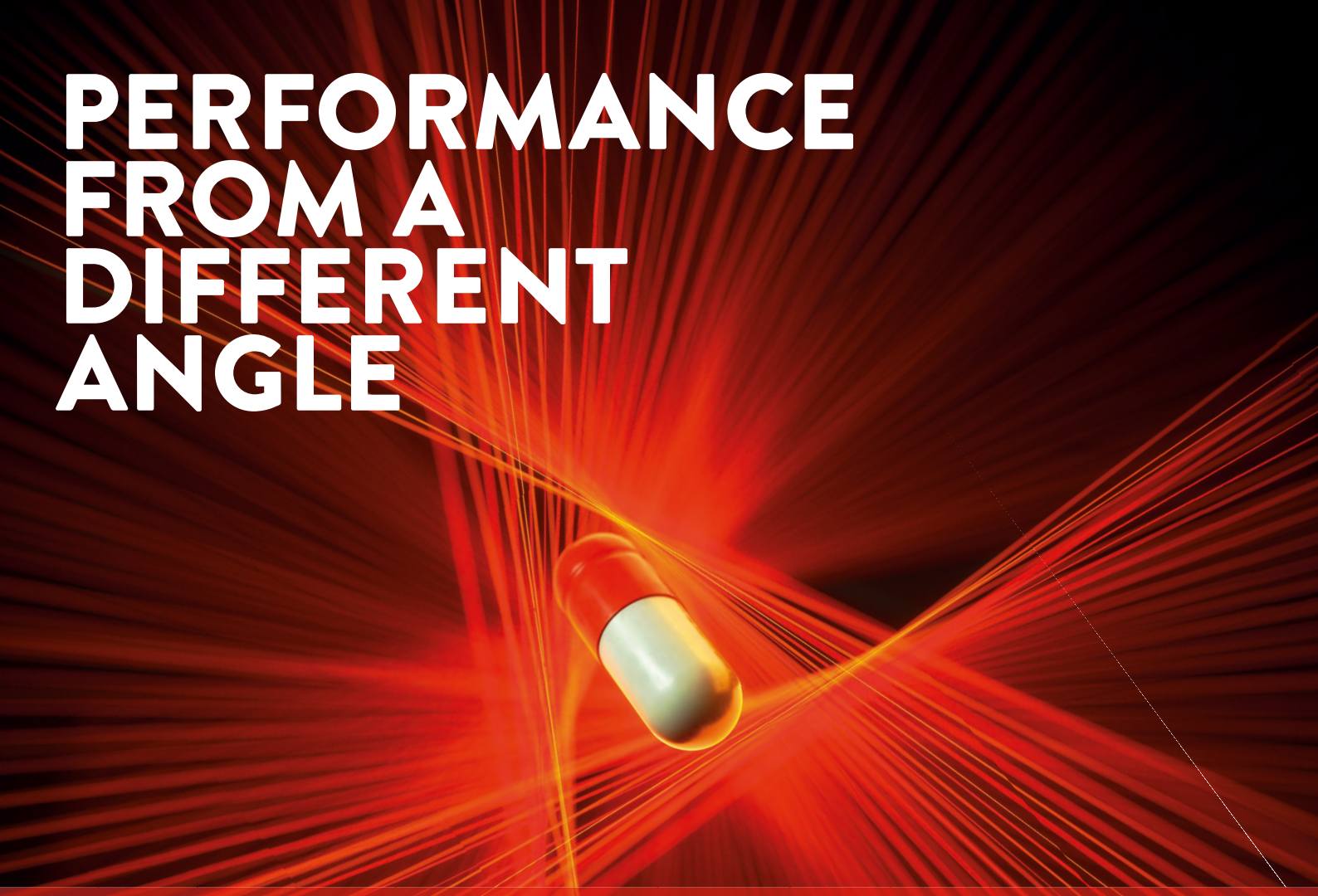
PERFORMANCE FROM A DIFFERENT ANGLE



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The Pharma Playground

Ups and downs, swings, merry-go-rounds… As ever, our industry will have to deal with its fair share of sociopolitical "fun" in 2019. What can we do? Address the challenges head on and celebrate the successes with verve.

As we move into the New Year, there is a great deal for the pharma industry to be excited about. Cell therapies are proving their worth and, buoyed by success, more and more companies are beginning to pile resources into the area. Gene therapies, too, continue to impress. Artificial intelligence, cloud computing, blockchain technology, on-demand manufacturing, and more are all marching defiantly into play. Doesn't it feel like we're surfing the crest of an innovation wave?

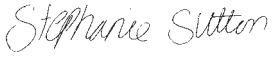
But there are also major challenges. Pricing and access to medicine aside, there is the more fundamental issue of the general public not respecting science or advances in medicine. Unbelievably, measles cases are at their highest in 20 years in Europe because of the anti-vaccine movement (1). The year 2018 saw over 70 deaths related to measles – double the number of 2017. Given that measles vaccination is proven to be both safe and effective, what a waste of healthcare resources – and lives – these figures represent.

Scientists in Germany say that a distrust of "power" can influence someone's choice of medical therapy (2). And a fair chunk of patients opt for homeopathic and naturopathic medications – the researchers found that almost 26 percent of Europeans employed complementary or alternative medical remedies at least once in a particular 12-month period. How ironic that (unhealthy) skepticism exists when it comes to proven vaccines, but can be totally absent for remedies utterly unproven by science.

Scientists themselves also sometimes help to muddy the water, when it comes to trust. At a conference organized by the Indian Scientific Congress Association, researchers decided to combine religious views and science; among other controversial presentations (which the organizers have since distanced themselves from), G. Nageshwar Rao, Vice Chancellor of Andhra University, claimed that ancient Hindus invented stem cell research and test-tube baby technology, citing Gandhari's 100 sons as proof (3).

Public perception, changing attitudes, repercussions of Brexit, political changes in the US, arguments about the value of drugs – they will all continue to rock the world of pharma. In some cases, there is little we can do but "ride" it out. But what we can do is acknowledge and confront genuine issues, while remembering to share success stories whenever we can. And that continues to be the goal of The Medicine Maker for 2019.

Stephanie Sutton
Editor



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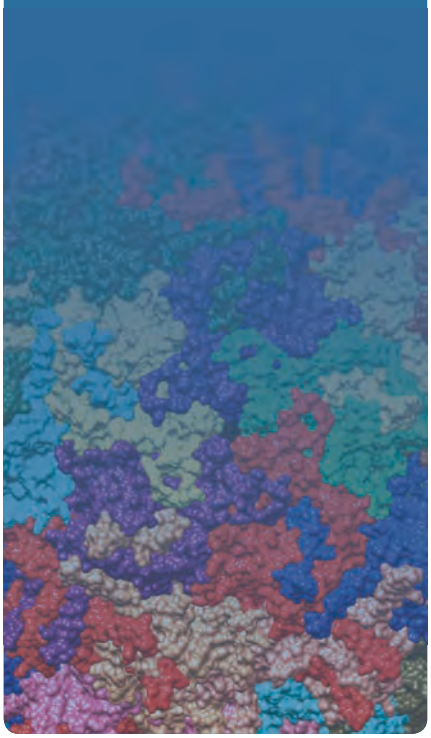
Upfront

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



Continuous Investment

How a collaborative project aims to cut the cost of gene therapy

Cobra Biologics, Pall, and the UK's Cell and Gene Therapy Catapult have won a shared grant of £1.5 million from the UK's innovation agency, Innovate UK, to investigate the feasibility of continuous manufacture of adeno-associated viruses (AAV) for gene therapy applications. Tony Hitchcock, Technical Director of Cobra Biologics, tells us more.

Could you tell us about the focus on AAV?

AAV is currently the main vector used to treat monogenetic diseases. The approach has shown spectacular results in the treatment of a broad range of conditions ranging from ophthalmic conditions through to whole body diseases, such as hemophilia and spinal muscular atrophy (SMA). We have seen the licensing of Luxturna for the treatment of retinal disease caused by the RPE 65 gene and it is anticipated that a number of other products, currently in phase III studies, will be successfully licensed in the coming months.

What are the main drawbacks with current methods for manufacturing AAV?

As with a number of other viral vectors, the production processes currently being used are essentially scaled up lab processes, using a number of steps that are poorly scalable and often inadequately defined, such as the use of adherent cell culture systems and ultracentrifugation for the separation of empty and full capsids. Going forward, the industry needs processes that are more suited to the anticipated amounts of material needed to address key disease areas, such as hemophilia, and to reduce the cost of manufacturing.

What are the expectations of the collaboration?

A specific requirement was for projects that could achieve greater than 25 percent improvements in process yields for vector manufacturing. To achieve this, we will be looking at all aspects of the downstream process, including vector recovery and high-resolution chromatographic purification steps.

This collaborative project is split into agreed interconnecting work packages, with each party bringing their own specialist knowledge and experience in vector production and analysis, working towards improving process yields throughout the AAV recovery and purification process. The work will not only be based on the adaption of processes to continuous manufacturing, where Pall are world leaders, but also through improved in-process analytics, which will be developed through expertise from the Cell and Gene Therapy Catapult.

What are the main hurdles?

The development of a continuous process is essentially a two-stage process. Firstly, we must transition from batch to continuous mode for the individual process steps. Secondly, we connect those operations. Our project will focus on the development of the individual downstream operations initially in batch modes, which will then be transferred to a continuous operation. The key hurdles will be to create well-defined separation steps and critical operational parameters relating to these separation steps, and then to establish the required in-process monitoring and process control strategies required to transfer to continuous operations. Here, development of the necessary in-process analytical tools will be crucial.

The real gap is that we are working with technologies that have been developed for the production of protein therapeutics (more specifically monoclonal antibodies), which are produced in suspension culture at multi-gram levels. Viral vectors are produced predominantly in adherent culture systems at

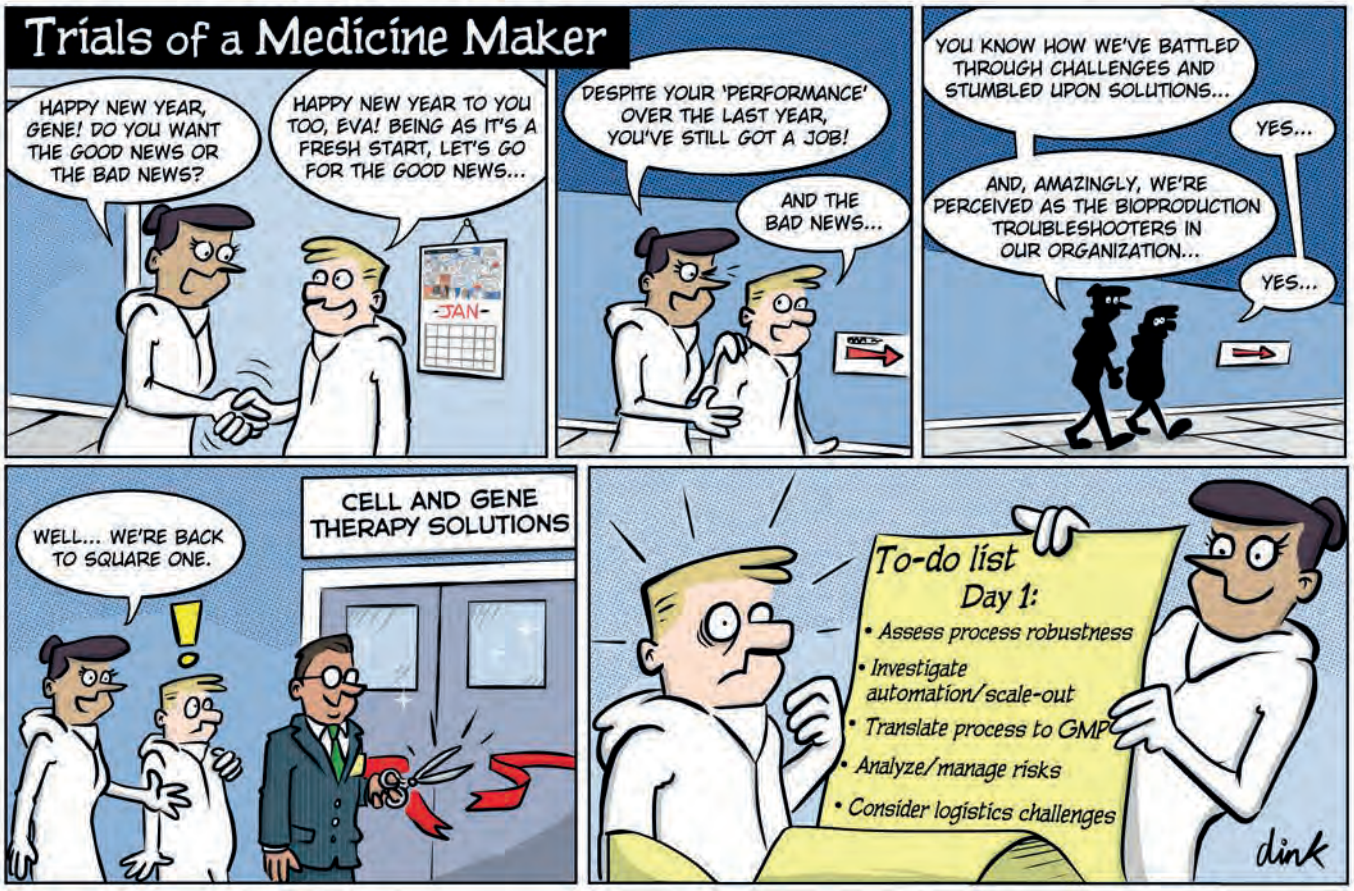
levels 5 to 7 logs lower titers and are physically up to 1000 times larger, generating micro/milligrams of product per batch. Therefore, we need to develop manufacturing technologies designed from a processing and monitoring perspective for these properties and product concentrations. Such considerations apply to both the upstream cell culture systems and the downstream recovery and purification platforms. For example, we need membrane technologies designed to recover and retain functionality of these particles rather than removal, and purification approaches that can achieve resolution between intact and partial vectors.

How does this fit the bigger picture?

There are a number of significant changes occurring in pharma – much of which relates to the need to reduce costs and improve access to new medicines, while trying to use new technologies and therapeutic approaches to address unmet medical needs and improve patient outcomes. In terms of new therapies, it is very clear that increasingly stratified approaches are being taken and this trend will continue, particularly as we see greater use of gene sequencing combined with AI (to target specific patient populations). Changes to clinical development strategies, in terms of the structure and nature of clinical trials, will also be required to reduce the cost and timelines for these studies.

From a manufacturing perspective, all of these factors point to the need for much more flexible approaches and platforms, to the supply of materials for clinical studies, and the ability to rapidly transition from clinical to commercial production. Significant changes in analytical and quality systems, as well as manufacturing systems, will be required to achieve this goal. Going back to the grant, the industry will need more innovative approaches, including continuous manufacturing, if we are to address these big challenges going forward.

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.



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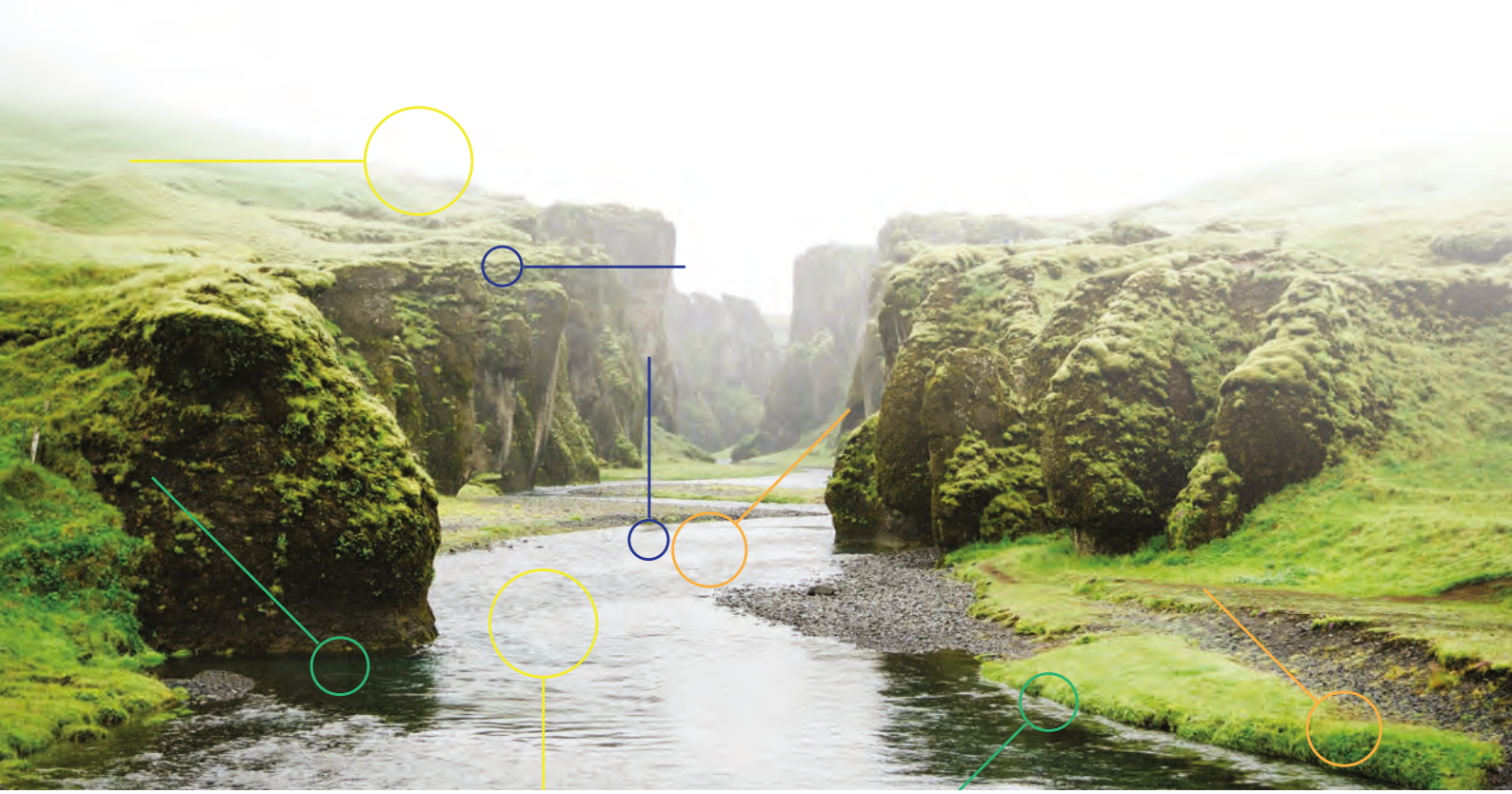

Proactive Policies

Gearing up for 2019, the EMA shares revised guidelines to better protect the environment, and unveils plans to protect us all in a health emergency

As our global populations grow and the demographics of the developed world change, the pharma industry is beginning to feel the strain. The pharmaco-economic burden of catering to the healthcare needs of the masses is spiraling, but the European Medicines Agency (EMA) is not idly standing by.

The environment at risk

Twelve years after the release of the original document, the EMA has published a revised version of its "environmental risk assessment (ERA) of human medicines" for a 6-month public consultation. The purpose of reissuing the document was to help clarify when ERA studies are required and improve the consistency of these assessments (1).

Biologically-active pharmaceuticals can enter the environment in a number of ways, including through manufacturing discharge, human use, and inappropriate disposal, and have been shown to directly affect wildlife. As one example, the API in the contraceptive pill has been found to feminize some male fish. The guideline aims to protect aquatic and terrestrial ecosystems including surface water, groundwater, soil and secondary poisoning, as well as microbial communities in sewage treatment plants. In Europe, an ERA is mandatory for any pharma company submitting a marketing authorization application and should be based on "the use of the product and the physico-chemical, ecotoxicological, and fate properties of its active substance."

The revised guidelines include:

- A detailed decision tree to provide more thorough technical guidance to applicants.
- Introduction of the term "endocrine active substances" to include all compounds that affect development or reproduction.
- Additional guidance on secondary poisoning (the exposure of predators to pharmaceuticals through the food chain).
- Suggestions to limit laboratory test methods to reduce the burden of testing on applicants.

The guidelines also encourage applicants to share data generated for the ERA to avoid the repetition of studies.

Stakeholders wishing to comment on the guidance must do so by June 30, 2019. Further details are on the EMA's website (1).

Emergency protection

The Spanish Flu outbreak of 1918 affected lives on a global scale. One hundred years later, despite advances in healthcare and pharmaceutical interventions, the threat of cross-border disease outbreaks still looms. The last decade – with outbreaks of H1N1 virus, Ebola and Zika – has proven just how real and present the danger is.

In line with its strategy for 2022, the EMA has prioritized planning for, responding to and communicating on

serious health topics, and has published a plan of how the agency would respond to health emergencies, whether it be infection, chemical, environmental or "of unknown origin". Building upon the 2006 pandemic influenza plan, the document reflects upon information gained during the 2009 influenza pandemic and the 2014 Ebola crisis to ensure readiness in dealing with emerging health threats (2). Some of the key aims of the plan are:

- To initiate and coordinate scientific and regulatory activities by involving all interested parties within the EMA and the European Medicines Regulatory network.
- To manage and coordinate the discussions on development, authorization and surveillance of relevant medicinal products, such as vaccines and antivirals for pandemic influenza.
- To effectively communicate relevant information to healthcare professionals, patients and regulatory partners.
- To provide support to international partners, such as stakeholders involved in the research and development of medicinal products, as required.

The document outlines three different levels of health threat plan, which translate into different levels of EMA staff involvement; Level 4 represents the highest level of threat (pandemic).

The processes stress the importance of continued and frequent dialogue within the European region and industry. Though the plan details the regulatory activities that the EMA would initiate during a disease outbreak, it does not cover how manufacturing issues related to specific medicines would be dealt with.

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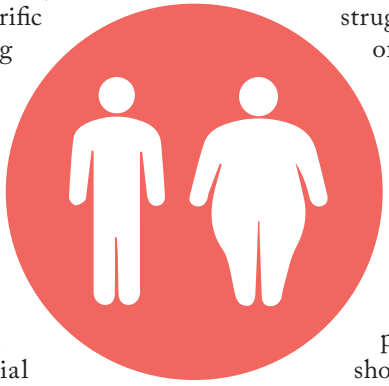
Bon Appetit?

Scientists continue to unravel obesity – and seek new drugs to control weight gain

The number of obese adults has tripled since 1975 (1), resulting in increased pressure on healthcare systems worldwide, and starting a race for new drugs that can control weight gain. The spiral of bad diet choices and lack of exercise can certainly lead to obesity, but it's also known that some people struggle more than others to lose weight. Damien Keating, a principal research fellow at Flinders University, and Beverly Rothermel, Associate Professor at The University of Texas, Southwestern Medical Center, are investigating RCAN1, a gene associated with Alzheimer's disease and Down syndrome that may also be linked with the weight loss process. Here, they share details of their research.

What makes obesity such a complex challenge?

Our world and lifestyles are changing. Whether it be improved economic status or the accessibility of cheap foods, our calorific intakes are increasing and affecting our weight statuses. However, it goes without saying that the pandemic of obesity is a complex issue and can't simply be reduced to overeating.



This multifactorial issue hasn't been fully explored and so our knowledge is still evolving. We do know that our exposure to diet and exercise in early childhood can affect our weight. But understanding why it is more difficult for some people to lose weight than others leaves us scratching our heads.

Regardless of the underlying causes for obesity, the individuals who struggle with it are all at risk of developing conditions that affect the quality of their lives. It's not uncommon for the obese to develop conditions such as heart disease, diabetes and some types of cancer. Therefore, by preventing obesity we should be able to reduce the burden on healthcare systems.

What role does RCAN1 play in obesity?

RCAN1 isn't a new protein on the scene. But our research has given us a unique insight into the ways this protein can affect human health. It is highly expressed under stressful situations – reactive oxygen species, high extracellular glucose levels and even amyloid beta plaques associated with Alzheimer's disease can boost the levels of RCAN1 in the body.

We have found that RCAN1 is potentially important in the regulation of body weight and fat mass. And by disrupting its expression in the metabolic tissues of mice, we have observed that they are able to burn more energy than normal mice while consuming a high fat diet. Their energy consumption was not due to increased activity or because they ate less – they simply burnt more energy while at rest.

RCAN1 inhibits non-shivering thermogenesis (a metabolic process confined to fat cells, controlled by the sympathetic nervous system). RCAN1

elicits its effects by transforming white adipose tissue into brown. White adipose tissue has a broad spectrum of functional applications in the body, but it is unable to oxidize the fatty acids within its adipocytes as quickly as brown adipose tissue. Obese patients typically have more white fat cells than average.

How could your research be translated into a pharmaceutical product?

Being able to burn calories at rest is of massive benefit to patients. Our current goal is to develop a series of compounds that target a key aspect of RCAN1 function with the aim of testing their usefulness as future anti-obesity drugs. These drugs may have the potential to be used in conjunction with other anti-obesity drug classes and with traditional approaches, such as exercise and diet.

Some media outlets suggested your work could lead to a pill that makes moderate eating and physical activity unnecessary. What are your thoughts?

It is unrealistic to believe that any form of medication alone will be the best approach to permanently changing a person's weight. After all, bariatric surgery, though effective, doesn't prevent a patient from putting on weight if they are unable to manage their diet or partake in regular physical activity.

It would also be remiss of anyone to suggest that a poor diet and lack of exercise would be advisable in any situation. The health risks associated with poor diet such as high cholesterol and atherosclerosis, or the poorer mental health outcomes and increased frailty in elderly individuals associated with reduced physical activity, cannot be avoided by relying on medication alone. No matter what pharmaceutics are on the market for weight loss, we should always promote proper diet and exercise.

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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

Remember Your Cleanroom Ps

When it comes to the crunch – the swab test – planning and preparation are key to best performance.

By Sue Springett, Sourcing Manager, Idorsia Pharmaceuticals, Switzerland.

There's an (in)famous British Army acronym – the 7 Ps: proper planning and preparation prevents p**s poor performance. The version used in the business world is slightly less fruity, but the message remains the same (proper planning and preparation prevents particularly poor performance). The statement applies to all areas of pharma, from business operations, right down to technical aspects, such as facility design and manufacturing activities.

The 7 Ps are memorable and I like to use them a lot in my role when discussing cleanrooms. A cleanroom is a huge investment and it needs to remain fit for purpose over the years, as well as meeting the needs of all that will use it. To get the investment right, proper planning is a must because there is no one-size-fits-all cleanroom, or even clean down processes. Changing areas and packing will also differ between cleanrooms, so you need to carefully consider your needs and plan effectively.

The first stage of planning is to consult with all stakeholders. The wisdom of the crowd is a really useful way to identify issues that might be missed at a purely conceptual level, so discussions should be had with senior management as well as project managers and everybody who uses the cleanroom on a day-to-day basis, as they will have the deepest insight into what can help or hinder their productivity. In practice, this approach can help factor out previous problems, which in turn has the potential to reduce risk; for example, simple positioning of furniture may offer better access for improved clean down.

Next, consider how the usage of the cleanroom could change over time. I've seen many companies opt for a fixed "showroom" finish, but this could be a costly mistake if the business has to pivot. The only thing we can be certain of? There are no certainties! The industry as a whole is being rocked by waves of technology-led disruption, while global finance and geo-politics remain in a parlous state. In short,

"The manoeuvrability of the furniture is key in terms of accessing all areas for thorough clean down."

it pays to play it safe, so flexibility is key. Working backwards from the SOP, a modular approach takes a core standard – for example, using a common working height or designs to support air flow – and can offer greater flexibility on where furniture is placed. The space can be quickly reconfigured to support growth, new processes, or integrate new equipment in line with changes in product development. Such a strategy also plays into the trend for "hoteling," whereby spaces are shared by multiple teams. With that goal in mind, cleanrooms need to be updated as quickly as possible and on an ongoing basis. By far the easiest way to support such communal working spaces is through the use of lightweight, free-standing furniture.

A further benefit inherent in this model comes down to the practicalities of the cleaning process. The manoeuvrability of the furniture is key in terms of accessing all areas for thorough clean down. It's important to remember microbial contaminants, such as bacteria, won't just take up residence on the item of furniture itself. It's hugely important to be able to clean all of surrounding areas. It's easy to overlook the obvious; something as simple as providing easier cleaning access can have a significant impact on swab test results. Aside from surrounding areas, swab testing almost always reveals design flaws in furniture that pose a significant risk for microbial contamination.

Be certain the furniture you choose is not at risk of deteriorating from detergents or disinfectants and is also suitable for your chosen sterilization processes. In the latter case, if you're using chemicals, such as VHP, furniture needs to be robust enough – ideally 316 grade stainless steel – so it won't degrade over time. If you are using an autoclave, you also need to consider the practicalities – can each item be easily disassembled and reassembled, for example?

Tables, trolleys and shelving aren't perhaps the most thrilling considerations when planning a cleanroom. However, when you're spending so much time and money on a project it really does pay to spend some time focusing on the minutiae. In my view, you can never be too thorough when it comes to planning the design of your cleanroom – and that includes the furniture.

China's Changing Future

The Chinese pharmaceutical market is already more advanced than many in the West imagine – and it only looks set to go in one direction.

By Minzhang Chen, CEO of WuXi STA Pharmaceuticals, China.

It is a special time in the development of China's pharma market, with the rapid growth of domestic companies aiming for international markets, and emerging R&D and biotechs opening up to develop new innovative therapies locally. Over the past decade, I've seen a vast number of Chinese-born scientists returning home after successful international careers; they are now creating an exciting R&D environment in their home country. This influx of resources, coupled with greater healthcare investment in China, has created fertile ground for biotechs looking to secure funding. At the same time, the NMPA (the former CFDA) has been harmonizing China's regulations with global standards, and streamlining drug-approval processes. The culmination of these changes is that an increasing number of biotech targets are advancing through clinical development, and greater numbers of international companies are looking to reach patients in China.

Changes in the Hong Kong stock exchange listings policies are also further fuelling opportunities for international and domestic partners looking to establish an Asian base. Domestic biotech companies in the pre-revenue stage can now list in Hong Kong – but, perhaps more importantly, a change to allow dual-listing for EU/US biotechs in partnership with a Chinese-based biotech will open up many opportunities for international companies.

Going back just ten years, the domestic sector's focus was almost solely on API production, whereas today the industry is now extremely diverse – a very different situation. Chinese pharma has rapidly advanced up the pharmaceutical development value chain, producing everything from novel "made in China" APIs, to finished dosage formulations, to innovative biotherapeutics. I believe that one of the most significant changes is the recent shift towards R&D in China. The government is determined to spend more on healthcare, as well as developing national pharma companies, in line with

the expectations of an increasingly middle-class population. Massive amounts of money are being put towards R&D at both a national and local level, and tax incentives are offered to companies pursuing R&D. The ultimate goal is to put China on the map as a creator, not just a supplier. From the inside, it's clear to see this change is already occurring; for example, there are now more CAR-T companies and ongoing trials in China than in the US.

The strategy is broadly outlined in "Made in China 2025," which marks the pharmaceutical industry as an area where there is potential for reinvention and growth (see a recent feature article from The Medicine Maker that delves deeper: http://tmm.txp.to/0119/China). Ultimately, the Chinese government aims to increase pharmaceutical output and increase innovation. One aspect of this plan, the marketing authorization holder (MAH) pilot, is an initiative that allows license holders of a drug to sell in China using a contract manufacturer, instead of being required to manufacture the drug themselves. The MAH is already helping to drive market innovation, not to mention facilitating rapid growth in China-based CDMOs.

The MAH also advances time to market for many global companies – so, it's proving to be beneficial internationally as well. There's a perception that US biotechs tend to keep their products at home in early development, but we have a huge number coming to work with us here in China in early development in light of our ability to expedite development timelines.

In recent years, the CNDA has made significant changes to accelerate drug approvals, and foreign drug-makers will be able to file a new drug approval using data from international, multicentre trials – in the past, a specific Chinese trial would often also be required. At the same time, there's also been a change in regulations to make it easier to register as a clinical trial site. And that means we should see improved access to newer drugs for domestically prevalent conditions being approved for use in China. Increasing numbers of Chinese companies are now running clinical trials for drugs in both the US and in China simultaneously.

China still has work to do to create more globally competitive pharma companies, but I believe China is already further ahead than is sometimes appreciated in Western markets! China has already seen a proliferation of successful pharma innovators in the country, with notable examples including BeiGene, Zai Lab and Hutchison China MediTech. BeiGene has been particularly successful, developing immune checkpoint modulators and PARP-inhibitors. Similarly, we have recently supported the commercial launch of Ganovo – a novel treatment for hepatitis C – in partnership with Ascletis. The partnership was made possible by the MAH pilot, showing just how important the new regulations can be in pushing Chinese companies to produce innovative therapies! Expect to see more examples like these as the changes currently taking place in China continue over the coming years.

Biotherapeutic QC: Time to Meet MAM

How high-resolution mass spectrometry (HRAM) and the multiple attribute method could give a boost to biopharma analytics, particularly with continuous processing on the horizon.

Simon Cubbon, Senior Global Marketing Manager for the Connected Laboratory, Thermo Fisher Scientific.

The well-known clinical benefits of biologics come at a price: large molecule drugs are highly complex, leading to analytical challenges throughout the development pipeline – from discovery, through to bioprocessing, quality control and release. Monoclonal antibodies (mAbs) and other complex drug products, such as antibody-drug conjugates (ADCs), must be exhaustively characterized to ensure the safety and efficacy of a batch before release. Even the smallest change or post-translational modification, such as oxidation, deamidation, or glycosylation, has the potential to render the drug batch ineffective, or worse, create negative off-target effects for the patient.

"Process development also faces challenges that are unique to the bioproduction environment."

Process development also faces challenges that are unique to the bioproduction environment, which, when combined with technological limitations of selectivity, fluidics and sterility can create an arduous

sample analysis process, if the correct methodologies are not carefully chosen.

Characterization of biotherapeutics typically requires multiple labor intensive or time consuming analytical techniques in offline QC labs; for example, cation-exchange chromatography, imaging capillary isoelectric focusing, and capillary electrophoresis sodium dodecyl sulphate (3). Typically, each technique provides information on only one or possibly a handful of critical quality attributes (CQAs) – and only after significant analysis.

In my opinion, high-resolution accurate mass (HRAM) mass spectrometry (MS) coupled with high performance separation represents the cutting-edge of biotherapeutic characterization, not only because it offers high-resolution data and impressive levels of sensitivity, but also because it increases confidence in results. Although MS is integral to biopharma R&D processes, its use is still evolving in bioproduction and QC (4). Why? Historically, HRAM MS has required skilled users to operate the instruments, sample processing has been slow and complex, and software hasn't always been up to scratch. And although HRAM MS certainly results in high resolution data, the fact that it still focuses on single or a handful of attributes makes it difficult to scale up to fit commercial bioprocessing and QC needs (5). Ultimately, these barriers to adoption have been too high to implement in QC and lot release. However, the situation is starting to look very different thanks to new and improved analytical systems and software – and a market place hungry for new solutions.

A relatively new analytical approach that is particularly well suited to biotherapeutics QC is the multiple attribute method (MAM) – and a number of research papers back its advantages (1). MAM is based upon traditional peptide mapping; the biotherapeutic must first be digested into peptides – a critical step that requires 100 percent sequence coverage, high levels of reproducibility, and minimal process-induced modifications (for example, deamidation). The resulting peptides are separated using liquid chromatography, and detected with HRAM MS, before being processed using software tools. High resolution MS with MAM provides a comprehensive view of the CQAs present in biotherapeutics, down to the individual amino acid sequence of each molecule. Detailed information can then be obtained on post-translational modifications (PTMs), glycoprotein structures, the presence of any sequence variants at extremely low levels, and minute amounts of potential process impurities (2, 4). In short, MAM has the potential to consolidate multiple analyses from QC to batch release, enabling us to work towards consistent biotherapeutic structure from batch to batch, and across the entirety of the process.

"Expanding the use of MS beyond R&D will not only reduce the number of experiments required per sample, but will also save time and resources."

For some time, there has been discussion about the need to improve biopharma manufacturing processes, and a common thread is the need for continuous manufacturing and real-time lot release, as alluded to within ICH guidelines (5). To get there, we need effective – and online – analytical methods for process monitoring and data generation. Here, MAM's ability to simultaneously characterize multiple attributes could provide comprehensive and timely support for the consistent flow of products from continuous processes, assessing quality and ensuring proper control.

Regulators encourage the use of new and improved technologies, but until there is regulatory acceptance of MAM, the technique must run in parallel with existing methods to prove its equivalency and demonstrate its key benefits. There is certainly work ahead, but I do believe it's time for HRAM MS and MAM to start moving into new areas – in particular, QC. Expanding the use of MS beyond R&D will not only reduce the number of experiments required per sample, but will also save time and resources – and provide increased confidence throughout the development and testing lifecycle.

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Single-Use That's Ready When You Are

Biopharma has embraced the benefits of single-use, but with a growing number of available components and highly customized assemblies, the supply chain becomes quite complex. Merck KGaA has designed a new program offering customized single-use assemblies with reduced lead times, and an enhanced level of supply security.

Sara Bell is fortunate to have been on both sides of the fence, spending 11 years in operations at Amgen before joining Merck KGaA, where she is now Senior Marketing Manager of their single-use portfolio. Sara knows full well the challenges faced in biopharma manufacturing – and why single-use is seeing increased uptake. Here, we talk to Sara about trends in single-use systems and why supply security of these products is critical to drug manufacturers.

What are the pros of single-use?

I would highlight four key benefits. The first is flexibility, which is really beneficial to multi-product facilities and contract manufacturing organizations (CMOs) that need to produce a variety of different products at different scales. Demand for those products can change rapidly, so being able to adapt quickly – which single-use allows – is a huge advantage. Secondly, single-use helps lower costs by reducing plant footprints and upfront capital spend. For emerging markets looking to get into the biopharmaceutical market, single-use is a great option because it requires less investment than a traditional stainless steel plant. The third benefit is speed. It's often faster to get a product to market using single-use. There is no need for clean-in-place or steam-in-place, and no need for validation of these operations, which greatly reduces the time it takes to get a facility up and running. Finally, single-use reduces your risk profile in terms of contamination. As the name suggests, once you use the product you throw it away and install a brand new sterilized assembly, so the risk of product carry-over is completely eliminated. In addition, due to the closed nature of single-use, you have better biological and viral contamination control.

And the cons?

There are risks and considerations to evaluate when implementing single-use, but I firmly believe that the benefits outweigh the risks. So, what is keeping drug manufacturers up at night when it comes to single-use? One of their biggest concerns is supply security. With traditional stainless steel manufacturing, the amount of consumables needed to run a process is limited to cell culture media, process chemicals, resins and filter elements. Additionally, production plans are primarily driven by turn-around time, or the time it takes to clean and sterilize vessels between batches. With single-use, the amount of consumables needed to run the process significantly increases, which makes the supply chain, especially procurement and inventory management, much more complex.

Many single-use suppliers use proprietary components, such as films, connectors and tubing – as well as their own technologies and assemblies for bioreactors, mixers and automated systems. Such non-uniformity means that it can be very challenging for end-users to dual source the consumables needed to run their processes. Therefore, they are forced to manage the risk by holding large quantities of safety stock, or performing tests to justify that two different products are "like for like". Varying supplier lead times and delivery delays can also impact production plans. These are challenges that we have sought to address through the Mobius® MyWay program.

What's the story behind the Mobius® MyWay Program?

The single-use market has seen significant growth over the past 10 years, and is predicted to continue to grow at a double-digit rate through 2025. Like many other single-use suppliers, we began to run into capacity challenges and it was important for us to define a scalable manufacturing model that met or exceeded end user expectations in terms of lead times, delivery, quality and supply security. The Mobius® MyWay program, which launched in January 2017, came into being to meet those end user expectations. Essentially, the program offers three options for customized single-use assemblies.

The first option is Mobius® Stock, which covers catalog items and high-volume repeat custom assemblies. With this option, we maintain stock of the assembly part number on our shelf and deliver when needed, which allows end users to maintain less inventory.

Option two, Mobius® Select, allows end users to design configured assemblies from an optimized component library, and receive them within six weeks. We maintain safety stock of every component in this library, thus enabling fast and reliable delivery with an enhanced level of supply security. The third option is Mobius® Choice, which allows end users to design customized single-use assemblies using our full Mobius® component library, and receive them with a traditional lead-time of 12–14 weeks.

Many single-use suppliers have chosen to address capacity challenges and custom business complexities using a different approach, by defining pre-configured standard assemblies. They offer solutions that they think end users will want. From our experience, no matter what you expect the end user to want, they will always want something slightly different! The Mobius® MyWay Program allows end users the flexibility to design a custom assembly and decide when they want to receive it.

Mobius® Select has been particularly popular…

Yes – and for good reason I think. If you look at the global market today, there are many dynamics impacting the biopharma industry. To remain competitive, drug manufacturers must examine how to cut costs, as well as how to increase flexibility and productivity. Biosimilars, emerging markets, novel therapies and next generation processing are just a few of the variables driving greater adoption of single-use. Many users are designing customized assemblies, using different components, from a variety of suppliers. It's gotten quite complex for end user networks to manage, so many are now looking to standardize and harmonize their single-use assemblies, by defining a set of preferred components – essentially a design space that they use to develop new assemblies. The Mobius® Select library provides them with just that; an optimized design space of pre-qualified components backed with supporting quality documentation and a growing dataset of extractables, tested per the BioPhorum Operations Group (BPOG) protocol. This significantly reduces the amount of testing required by the end user, and enables them to implement single-use faster. The six-week lead time allows end-users to hold less inventory and be more nimble with their production planning. And the biggest benefit with Mobius® Select is that it still gives end users the flexibility to customize their assembly, across a broad range of applications, to meet their specific processing needs and requirements.

How has the industry reacted to the new offering?

We saw adoption pick up significantly mid-2017. We find that once an end user experiences the entire process from the design of their assembly through to order receipt, they realize the value that Mobius® Select can provide – not only in terms of delivery time, but also in terms of quality assurance, reduced inventory costs, time savings, flexibility, and security of supply. These benefits drive the creation of new Mobius® Select assemblies and have also prompted end users to reach out to us with specific requests; for example, "I have X number of existing assemblies from Merck KGaA or a competitor. Can you help me transition these to a Mobius® Select design? What components would I need to tweak to make this Mobius® Select compliant?" For common applications like mixing, storage, transfer and filtration, typically only minor component or tubing length changes are needed to make a design Mobius® Select compliant.

The program has proved to be very successful for both us and end users. The aim of the Mobius® MyWay Program was to meet drug manufacturers needs in terms of fast and reliable delivery, easing the implementation of single-use, and increasing the level of quality and documentation that they receive with the product. But the solution we came up with also enabled us to scale our manufacturing operations to ensure we can support the continuing growth of single-use through 2025 and beyond.

We are going to continue to enhance the program and evolve the library based on market needs. Towards the end of November, we are launching a web-based interactive tool that will allow end users to see which components are available in the Mobius® Select library. For more information on the program, or to request the help of a single-use specialist, I encourage readers to visit merckmillipore.com/singleuse-myway. To directly link to the Mobius® Select tool, you may visit mobiustool.com

HERE'S TO NEW BEGINNINGS

Conversations around drug pricing look set to continue for years – and the resulting pressure will undoubtedly necessitate change. And yet, despite controversies surrounding this thorny issue, we should not forget to celebrate the positive side of pharma: fantastic progress in science and engineering is driving advances in discovery, development and manufacturing, with life-saving – and perhaps industry-changing – results.

By Stephanie Sutton

THE GURUS

Business leader
Annalisa Jenkins

Chief Executive Officer, PlaqueTec

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Not-for-profit
Steve Arlington

President, The Pistoia Alliance

Technology supplier
Olivier Loeillot

Senior VP, BioProcess, GE Healthcare Life Sciences

CDMO
Elliott Berger

Vice President, Catalent Pharma Solutions

WHAT WERE THE HIGHS FOR PHARMA IN 2018?

Annalisa Jenkins: I feel very positive about our scientific progress. 2018 was marked by the acceleration of science, approval of disruptive new therapies and significant new capital entering the sector. The promise of advanced therapies, which leverage our enhanced understanding of biology and disease, was realized with the approvals of CAR-T and gene therapy products – which offer potential cures for devastating diseases. We've also seen new vaccines for Ebola, therapies for multi-drug resistant TB and new science addressing HIV infection emerge from collaborations between industry and philanthropy. Many major regulatory systems have also evolved to help deliver promising new medicines to patients faster. And then the translation of academic discoveries into new startups – some of which are receiving major funding rounds – has exceeded all previous records.

Markus Thunecke: For me, one of the big highs was the continued success of cell and gene therapies. There are now several products on the market and a rich pipeline of around 300 products. I expect to hear lots of good news over the next years for patients with rare and life-threatening disease, as well as an increasingly positive investment climate given the many large companies that have been "watching and waiting" when it comes to the cell and gene therapy field.

Like Annalisa, I believe it's been a very good year for scientific progress as a whole. 2018 saw a high number of FDA approvals: 59 as of December 21, compared to 46 in 2017, and a low of 22 in 2016. Alnylam finally brought the first RNAi product, Patisiran for hATTR amyloidosis, across the finish line. After years of ups and downs, this is a crucial sign for the whole field of RNA therapy. The field of checkpoint inhibitors was also recognized, with the Nobel Prize for Medicine honoring the scientific fathers of checkpoint inhibition in cancer, James P. Allison and Tasuku Honjo. The explosion of knowledge and clinical advances in the field of immune-oncology is one of the largest science-driven success stories the industry has seen in decades.

Elliott Berger: I'd like to add that the number of molecules in the pipeline has also increased from roughly 8,500 molecules five years ago to an estimated 12,000 in the pipeline today, targeting the broadest array of diseases ever. I think it's really encouraging to see so many accelerated approvals that are helping to bring new therapies to patients faster. There are high points in the manufacturing space, too. For example, in biologics, cell line production titers have increased enormously and the manufacturing process is becoming more efficient. In small molecules, enabling

technologies are maturing and helping bring more treatments to patients.

Olivier Loeillot: The immunotherapy market is a standout performer. In just a year, the global pipeline of immuno-oncology products saw a 67 percent increase in the number of active agents, and a 50 percent increase in active drug targets.

I also agree with Elliott; I'm delighted by the innovation being seen in manufacturing technologies. For example, there are prefabricated modular facilities that help cut the costs associated with building new facilities, and end-to-end, semi-automated manufacturing platforms that can help with cell therapy production. The magnificent biomanufacturing process intensification and capacity increase that we have witnessed during the past decade has been aided by flexibility brought about by new technologies in production. It's now possible to cost-effectively produce small batch sizes, which is important if we are to see more personalized therapies reach the market.

Steve Arlington: Generally speaking, industry critics are quick to say R&D expenditure is rising, output failing and development times increasing, but according to The Life Sciences Innovation Report, a new study from The Pistoia Alliance, development times are starting to stabilize and decrease, and more molecules are coming to market at a stable budget. In other words, the industry is getting better at developing drugs. Another high point is, as the others have mentioned, precision medicine, which is offering new treatment options for rare diseases, cancer and autoimmune diseases.

I am also really excited by the increased collaboration in industry, such as with academia and biotechs. Diversity is absolutely essential to make the most of new science, and the ability to think outside of a narrow knowledge base; none of us were brought up and taught about any of the exciting things coming through today.

AND THE LOWS?

AJ: In the high-risk world of drug development, not everything will be successful. The year was inevitably marked by failures of some science platforms and programs. It is bold and courageous to try and then fail, and alas we still have not developed a sector and system that incentivizes and rewards efforts addressing major global healthcare issues. Antimicrobial resistance is a threat to humanity; the opioid abuse crisis in the US continues to take lives on an unimaginable scale; and people living in some countries continue to die every day from preventable and treatable disease. Whilst we celebrate the achievements of remarkable science, we must continue to ensure that the diseases killing people worldwide and threatening our stable and thriving societies can secure support in the hearts and minds of governments and investors.

OL: The industry needs to improve clinical trial success rates. Recently, there have been too many terminations of immuno-oncology phase III studies, and drug development remains risky and costly. It takes an average of 12 years and costs almost $2 billion to bring a drug to market. Going forward, we need better diagnostic tools and biomarkers to identify the right patients for clinical trials and treatments.

EB: Industry's R&D productivity continues to be challenged. We have seen a large number of failures, even in later stage development, and a less visible but very high attrition rate in early phases. With pricing under pressure, the high spending coupled with high failure rate is a big issue. Industry needs to make progress on new approaches to clinical trials and development and formulation.

MT: As every year, it makes me sad to see the poor public reputation of the pharmaceutical industry. Although the majority of people in the industry want to do good things for patients, society, and their companies, a few bad actors can do massive damage.

SA: In some cases, cancer has gone from being a terminal prognosis for individuals to a chronic disease that can be treated quickly – and the quality of life can be high. More success is being seen every year, but some cancers lag behind. For pancreatic cancer, we seem to have gone nowhere in the last 25 years. We're also lagging in other key disease areas, such as Alzheimer's, although we are expanding our understanding.

Regarding Markus' comment about the reputation of the pharma industry, I'd also add that societal trust of healthcare, in general, is very low. The healthcare payer, provider and pharma companies all get smacked by the media and social media, and there will never be enough money to solve all the healthcare problems of the world. It is a constant balancing act between what a country can afford, and what society wants. In the UK, it was gratifying in 2018 to see the National Health Service and Minister for Health announce that they want to move to an agenda for teaching people how to keep healthy and prevent disease. I published an article (which was widely read and acclaimed back in 1998) about the fact that the NHS and healthcare providers could not survive if people didn't move to a prevention agenda. We can't afford to eat what we like, do no exercise, and so on, and expect somebody else to pick up the bill. It's been plainly obvious, and so one my frustrations has been why it has taken governments 20 years to catch up?

Speaking from the perspective of a technology provider, I believe that solution providers and biomanufacturers need to strengthen their partnerships. Transparency and exchange of information between the two should enable much faster and more economical product development and manufacturing. In particular, digital collaborations are becoming more popular.

2019 PREDICTIONS

Markus Thunecke: Mergers and acquisitions are common every year in the pharma industry and this will continue in 2019. Many large US pharma companies have significant cash reserves, but instead of just buying back shares and paying dividends, there is a strong rationale in acquiring successful biotech companies.

Steve Arlington: Speaking from the point of view of someone based in the UK, if there ends up being a hard Brexit then the industry in the UK will change as the country becomes very insular. Many challenges will be faced, including the most basic ability to get the necessary drugs, devices and materials needed to run healthcare. And then there is the question of what it means for global collaboration. We need to be collaborating and bringing new datasets together to research difficult diseases and develop new drugs.

For a positive scenario, I'd love to see us make a big breakthrough in understanding the underlying pathology of Alzheimer's disease or some pathology that will affect other diseases of the central nervous system.

Olivier Loeillot: Biosimilars product sales will pick up tremendously in 2019, considering all the recent approvals, and I think these therapies will offer increased medicines access for patients, whether in the US, Europe, China or India.

I also expect to see more precise, targeted therapies for smaller patient populations being developed. Many exciting drug innovations are coming from smaller companies, including start-ups, and more funding is starting to pour into the area.

Elliott Berger: Speed to market will continue to be a consistent and growing theme. The FDA's Accelerated Approvals programs tend to grab headlines, but this is not just a US phenomenon; regulators worldwide are creating guidance and policies to safely test novel technologies faster. Product differentiation is another huge concern with many medicines failing to make a difference to patients and earn adequate returns. The industry will make an effort to address both by better understanding the real-world impact of treatments, and boost collaboration to developing more products and improved treatments.

WHAT ARE THE MOST EXCITING INNOVATIONS AFFECTING THE (BIO)PHARMACEUTICAL INDUSTRY RIGHT NOW?

AJ: We are living in an age that is redefining disease. Our understanding of biology, pathways and new targets is accelerating and leading us to realize the vision of personalized medicine. A major disruptor today – which will continue in the near future – is our increasing ability to gather, curate and analyze huge volumes of data. From basic research through to discovery, into the clinical development and healthcare delivery space, the application of AI techniques is truly disrupting our industry and our ability to deliver on the promise of longer, healthier and happier lives.

MT: I agree; it really is an exciting time. Massive advances in the biological sciences are now happening extremely fast and our ability to interrogate large datasets with AI and other tools has reached levels that were thought impossible just a few years ago. Who knows what 2019 will bring? In terms of standout innovations, I find it hard to choose (which is a great sign!), but I would pick the promise of allogeneic Car-T therapy, simplifying a super complex supply chain and hopefully bringing down costs of goods and, ultimately, price. Allogeneic Car-T requires gene editing, and we have the tools available. CRISPR and other gene editing tools could change the face of the industry, or even medicine itself, over the next few decades, but these tools also raise ethical debates that will need to happen in parallel with scientific ones. Equally exciting is the prospect of Car-T/TCRs or modified versions thereof (with safety switches and so on) in solid tumors – something that has proven extremely difficult because of on-target off-tissue toxicities. The whole field of genetically modified cells in oncology reminds me of molecular Lego. It's a bioengineer's dream.

In terms of next wave innovations, I see much promise in the area of auto-immune disease. The massive investments into immuno-oncology will result in knowledge that is also applicable in areas that will require not only activation, but specific dampening of the immune response. Some companies have already started to routinely interrogate both the activation and inhibition of immune-checkpoints, to give just one example.

OL: Like Annalisa, I believe that AI and data will be very important in the future. In fact, data is already revolutionizing the manufacture of medicine. Many pharma companies today are particularly focused on digital manufacturing strategies and automation. This change is also evident when looking at our own, internal processes – we are, for example, running

> "ONE OF THE LARGEST BARRIERS, IN MY EXPERIENCE, HAS NOTHING TO DO WITH THE COMPLEXITY OF THE UNDERLYING SCIENCE AND TECHNOLOGY; IT IS TO DO WITH THE PEOPLE"

a major manufacturing project at our cell culture media factory in Logan, Utah, that combines lean and advanced manufacturing with software analytics. We are also including advanced data analytics that will help us and our customers to increase the understanding of the relationship between raw material variability and process performance during the manufacture of biopharmaceuticals. The ability to detect and monitor raw material variability through data integration will be an important step to ensuring consistent and predictable biomanufacturing performance.

SA: There are a huge variety of multidisciplinary innovations coming through pipelines, including new technical approaches to antibiotics, biospecific antibodies, effective antibody-drug conjugates, genome science, microbiome science, 3D printing, nanosensors, new imaging methods, machine learning, computational biology… the list goes on. But we must take care not to get into the "continuous motion machine," where people start adding all of this great science together to come up with something ridiculous. Some believe that machine learning will allow patients to talk to a computer that will safely diagnose them and deliver a prescription – and that this will be possible in a matter of months. We are a very long way off anything like that!

WHAT ARE THE BIGGEST BARRIERS TO INNOVATION IN THE INDUSTRY?

AJ: I Innovation and progress rely upon a culture of collaboration across disciplines and geographies, so ideation can thrive among those who are willing to take risks. Open access to ideas and sharing of science and expertise across the continuum of research and development must be encouraged, and must move beyond the current geopolitical tendency towards nationalism (and physical and political borders). Life science and healthcare professionals will

KEY APPROVALS OF 2018

January:
- New drug, Hemlibra, for hemophilia A, the most commonly occurring form of the bleeding disorder (EMA). This is the first new medicine in over 20 years to treat people with hemophilia A with inhibitors in Europe.

February:
- First medicine, Amglidia, to treat diabetes in neonatal babies (EMA). The drug can also be used to treat newborns, infants and children.
- Erleada, the first drug approved for non-metastatic castration resistant prostate cancer (FDA).

March:
- Trogarzo, a new type of antiretroviral for HIV patients for patients with limited treatment options (FDA).

April:
- Crysvita, the first treatment for children and adults with x-linked hypophosphatemia (FDA).

May:
- Doptelet, the first oral drug to treat low platelet count in adults with chronic liver disease scheduled to undergo a procedure (FDA). It allows many patients to avoid platelet transfusion.
- Palynziq, novel treatment for the rare genetic disorder phenylketonuria (FDA).
- Second CAR-T therapy for the US (Kymriah) approved (FDA).

June:
- First two CAR-T cell therapies in Europe for the treatment of blood disorders, Kymriah and Yescarta (EMA).
- First drug in the US containing a purified substance from marijuana, Epidiolex for the treatment of epilepsy (FDA).

July:
- First drug for smallpox, TPOXX (FDA).

August:
- Poteligeo, new treatment for two rare types of non-Hodgkin's lymphoma (FDA).
- First RNAi therapeutic, Patisiran, approved in the US and EU (FDA and EMA).

September:
- Libtayo approved specifically for metastatic cutaneous squamous cell carcinoma, the second most common skin cancer (FDA).

October:
- Dengvaxia, the first vaccine for dengue fever (EMA).
- Namuscla for non-dystrophic myotonia (EMA).

November:
- Fexinidazole Winthrop – the first oral-only treatment for human African trypanosomiasis (HAT) (EMA).

December:
- Ultomiris, a treatment for paroxysmal nocturnal hemoglobinuria administered via a biweekly injection (FDA).

realize their shared purpose if they are encouraged and incentivized to collaborate across public and private government sectors.

MT: One of the largest barriers, in my experience, has nothing to do with the complexity of the underlying science and technology; it is to do with the people, mind-set and culture of biopharma companies. One of the root causes of the R&D productivity crisis in large pharma has been the inability of large organizations to leverage the creative potential of its incredibly skilled work force in R&D. And that's one reason why most breakthroughs come from small to mid-size companies; and those who are successful find it difficult to maintain as they go through a period of hyper-growth (the story of the current crop of outperformers Gilead, Biogen, Celgene or Regeneron).

SA: The sheer cost for single organizations to discover a target and develop a drug remains a problem – and there are fewer and fewer organizations with the financial and intellectual ability to do this (partly because consolidation in the industry is reducing the number of R&D groups). But, on

the plus side, there are many small startup companies, who collaborate with experts to find the best way forward. Here, however, the sharing of data can be an issue. I believe we need more pre-competitive collaboration – and companies need to realize that it is much cheaper and effective to collaborate in an early stage without getting themselves into trouble with anti-competition laws.

EB: Increasing collaboration must be a priority in 2019. High attrition rates and the associated costs of development continue to hinder the industry, but open innovation could help us to share knowledge and optimize the relatively few candidates that will go on to be approved (and even fewer that will go on to be a commercial success). I think the pharma industry is fortunate in that there are many academic, development and commercial partners worldwide who can help – and there are also a lot of initiatives to improve collaboration. Many big pharma companies today have established open innovation platforms to better foster research. For drug development and drug delivery, we've also set up our Applied Drug Delivery Institute. The institute is based on open collaboration and allows partners to reach their own models for collaboration – it doesn't insist on being a partner or getting in the way of collaboration. The institute has published various articles and has its own publications to help share scientific knowledge.

WHAT OTHER BIG CHALLENGES ARE AFFECTING THE PHARMA INDUSTRY?

AJ: Small and mid-sized biotech companies comprise the lifeblood of scientific and medical progress around the world. We must ensure that capital flows into this sector to ensure that preclinical programs and platforms are funded from proof-of-concept through human studies. SMEs are driving the innovation engine and addressing the needs of patients globally. As new capital enters the sector, we need to ensure that we can connect talent and ideas with good quality capital, or too many of the SMEs will be sub-scale and unable to optimize their platforms' probability of success.

SA: There are challenges and trends that come from outside pharma development, which the industry still needs to understand and somehow react to. Affordability and the pricing of drugs and healthcare come into this category. When it comes to the cost of healthcare, most people criticize the cost of drugs, but the total bill for drugs across the healthcare continuum is usually only around 15 percent. In the UK, it's less than 10 percent. Drug companies are constantly dealing with the pressures of drug pricing and strong criticism, but everyone should be worrying about the remaining 85 percent of healthcare costs.

EB: From my perspective as an outsourcing provider, I'm seeing a lot of venture capital-backed, relatively small, capitalization companies. In fact, around 75 percent of the pipeline is coming from small and mid-sized companies. These companies do not have the resources of large pharma, although fortunately in today's industry there are many partner firms who can help – whether for early research, formulation, clinical programs, commercial manufacturing, or licensing and approval.

WHAT CAN THE INDUSTRY DO TO IMPROVE ITS REPUTATION?

AJ: The healthcare and life science industry offers daily hope to people globally. Society hears negative stories about pricing, access and profits, and less about scientific discoveries, patient support programs and the vast philanthropy fueled by pharma companies. We need to continue to raise awareness and celebrate the work and dedication of scientists, physicians and life science professionals. So much of what we do is hidden from view. We need to change the dialogue on pricing and access, and work together with societies globally to be part of the solution to ensuring that the work of our R&D organizations and academic collaborators is available to all those in need. We need to shift the notion that our industry puts profits before patients towards the reality of scientific and medical innovation that ensures longer and productive lives as a fundamental human right.

MT: I agree with Annalisa. Two things are crucial in my view. First, we must do more to educate the public about pharma's great success stories in addressing unmet need, and the complex networks of academics, biotechs and large pharma that were involved in moving them across the finish line. The cure for Hepatitis C, the fantastic successes in treating certain rare blood cancers through cell therapy, and the durable responses to checkpoint inhibition in some patients with metastatic solid tumors are three good examples – but there are dozens more.

Second, we must condemn unethical profiteering, and we must "walk the talk" when it comes to pricing of drugs or proving their economic value.

SA: A difficult question. For a start, our industry doesn't even know how to collaborate between its own organizations and associations. Before we can send a message out, we need to get the different cohorts of industry bodies talking with the same voice; unfortunately, the pharma industry is disparate and focused on intellectual property, which limits collaboration. Pharma companies are all very similar organizations but, once you start digging, you discover that everyone has competing or conflicting objectives. Business models also affect the therapeutic areas that companies target. Why is the pharma industry not spending a fortune on bringing new antibiotics

2018 PIVOTAL MOMENTS

The good, the bad and the stockpiled

The UK's news media has been dominated by talks of Brexit and the possibility of leaving the EU with a hard Brexit, or even no deal at all, which has led industries across the country (and that supply into the country) to make preparations to weather the potential storm. In an attempt to reduce the impending panic, the government began talks with UK-based drug companies about the cost of stockpiling drugs crucial to the treatment and survival of patients across the UK. UK Health Secretary, Matt Hancock, said the talks were essential and a "responsible part of planning for a no-deal" situation.

Challenging the norm

2018 was an interesting year for US citizens. Between government shutdowns and talk of impeachment, there has also been growing outcry at the cost of medicines, including generic drugs for critical disease. One ambitious company is attempting to tackle this issue. Civica Rx, headed by Martin Van Trieste, former quality control at Amgen, aims to be a not-for-profit generic company. Van Trieste's aim is to make the company "a public asset," ensuring that affordable medications are there for those who need them.

First Step Forward

The first CAR-T therapy was approved in the US in 2017, but for Europe the major approvals came in 2018 for Yescarta and Kymriah. Personalized immunotherapies work by modifying a patient's immune cells so that they can combat cancerous cells. However, access to these drugs may still be limited in some countries. The UK's National Institute for Health and Care Excellence, for example, initially rejected Yescarta, although later recommended it towards the end of 2018.

R(AI)sing Industry Standards

2018 can be considered the year for AI start-ups, with a number of companies looking to use AI to facilitate drug discovery. Companies like BenevolentAI and Atomwise are using neural networks to ensure the right drugs make it through the initial drug discovery screening steps and are securing partnerships with key industry players. E-Therapeutics, a UK based biotech firm, also entered a collaboration with Novo Nordisk in December 2018 for the development of new drugs for the treatment of Type 2 diabetes.

And the winner is…

Immunotherapy pioneers, James Allison and Tasuko Honjo, cinched the 2018 Nobel Prize in Physiology or Medicine for the development of a novel approach to treating cancer. Through the use of checkpoint inhibitors, the pair showed that a host's immune system could be manipulated to attack cancer cells. This work has revolutionized cancer research, prompting more treatments reliant on immunotherapies to be developed.

A green solution

Cannabis-derived products have been viewed with some scepticism for many years, but research in the field is heating up. In 2018, the FDA approved the US's first cannabidiol drug. Epidiolex, a treatment for Dravet and Lennox-Gastaut syndrome (two rare forms of childhood epilepsy) was available for use from June 2018. Other countries are also looking at the benefits prescription cannabidiol could offer to patients.

To edit or not to edit? That is the question.

CRISPR gene-editing technology came under increased scrutiny at the end of 2018 due to a clinical trial carried out by Jiankui He. The associate professor from the Southern University of Science and Technology in Shenzhen edited the genomes of twins, Nana and Lulu, before they were born in an attempt to develop HIV-resistance in the infants. The experiments took place without the approval of the university and resulted in the dismissal of the researcher from the university. The experiment is considered a point of "no return" for the CRISPR field.

to market? The answer is because they will not be rewarded for doing so. Media outlets and politicians bang on about the lack of innovation in certain areas, but it is within their ability to add incentives and to change intellectual property laws. It is much easier, however, to point the finger of blame at the pharma industry (and in politics, this leads to votes). The trust issue doesn't squarely sit on pharma's shoulders – politicians also need to be honest about drug costs and how the system works.

OL: There is a need for greater collaboration across the pharma industry. We should strive to create a more holistic industry with a strong focus on areas of public concern. I would like to see the industry engage more in a public discussion, sharing knowledge and ensuring that scientifically accurate and validated information is out there. We should be informing people about how pharma companies have transformed the treatment of many serious illnesses during the last decade.

EB: There are, without doubt, examples where players and practices have damaged the reputation of the industry. Coupled with the costs associated with high R&D attrition rates and the need to meet shareholder's expectations, it is perhaps no surprise that there are reputational issues. There are many technologies and partners that can help pharma companies improve R&D effectiveness and reduce cost. In my view, the industry needs to get better at predicting which candidates to advance, and which drug delivery systems will yield better treatments for patients.

However, we also need to celebrate our successes more. So many medicines that have saved millions of lives, from vaccines to antibiotics to painkillers, are taken for granted. New waves of medicines have acted on the central nervous system, offer treatment for viral and retroviral infections (e.g., HIV/AIDS therapies), and have cured or delayed the onslaught of cancers. New biologics-based medicines have been able to mimic or support key features of the immune system and we consistently see treatments emerging for illnesses that had previously been considered undruggable. I think pharma has a much better reputation in the eyes of those patients – and their families – who have been saved from debilitating or life-threatening illnesses.

WHERE SHOULD THE INDUSTRY'S PRIORITY LIE IN 2019?

AJ: In 2019, I hope the global focus of the life sciences industry will be on collaborating globally to accelerate the improvement of population health, wellness, and happiness. I hope we will see marked acceleration in the use of health data to deliver a more productive and effective sector, with new capital and players that are willing to take risks and make bold moves. We will see meaningful advances in personalized approaches to care. The immune system will continue to offer targets for disease prevention and cure. Cells as therapeutics will accelerate, as will the promise of bugs as drugs. And the final frontier of the brain will advance as new therapies for major mental health issues and degenerative disorders finally move through to deliver clinical data that offer hope for millions of people.

MT: Focusing on patients and their needs still is, and should remain, the top priority for the industry. There are literally hundreds of diseases in desperate need of improved therapies. Because of that, the industry has to become better and faster at translating science into differentiated medicines (Paul Janssen used to say "the patients are waiting"). We now have better tools than ever before (both scientific and computational), and with the right organizational model that motivates and empowers people to use their creative force, we can expect great things to happen over the next years.

EB: Certainly there are many ways in which the industry could still improve. I think there is a big win to be had by improving patient acceptance. It is a fact that many patients do not take their medication as prescribed, especially at the very start. Outcomes could be improved by boosting initial acceptance and ongoing adherence, which would also save enormous costs in healthcare. It is entirely within the grasp of the pharmaceutical industry to make a significant difference by focusing on drug product design from the very beginning of development. For example, with the technologies at our disposal today, there is no excuse for presenting patients with a large tablet several times a day to be taken only with food. Dose design was once considered a late phase activity, but must be considered early. This starts with selecting the best molecule variant, the best formulation type, finding the optimal dose form design, and goes all the way through to designing delivery devices and medicine packaging that are truly fit for patients' needs in today's busy world.

Our research indicates that only a quarter of R&D groups pursue a systematic approach to patient-focused drug design. The biggest challenge, however, is that the R&D teams making the crucial, early decisions about design may not have enough information on the real-world challenges experienced by patients, caregivers, and providers in administering treatments. We need to do better together.

OL: Supporting increased and better access to potentially life-saving therapeutics should be the number one priority for all of us. In practice, this means faster product development times and strong collaboration between pharma and technology providers. As a wider community, we have the tools and expertise we need to improve the manufacturing process and deliver better medicines. And going forward, our abilities will only be enhanced by new tools, such as digital and artificial intelligence. There are major changes happening in science and drug development that will help to increase life expectancy significantly in the coming decades.

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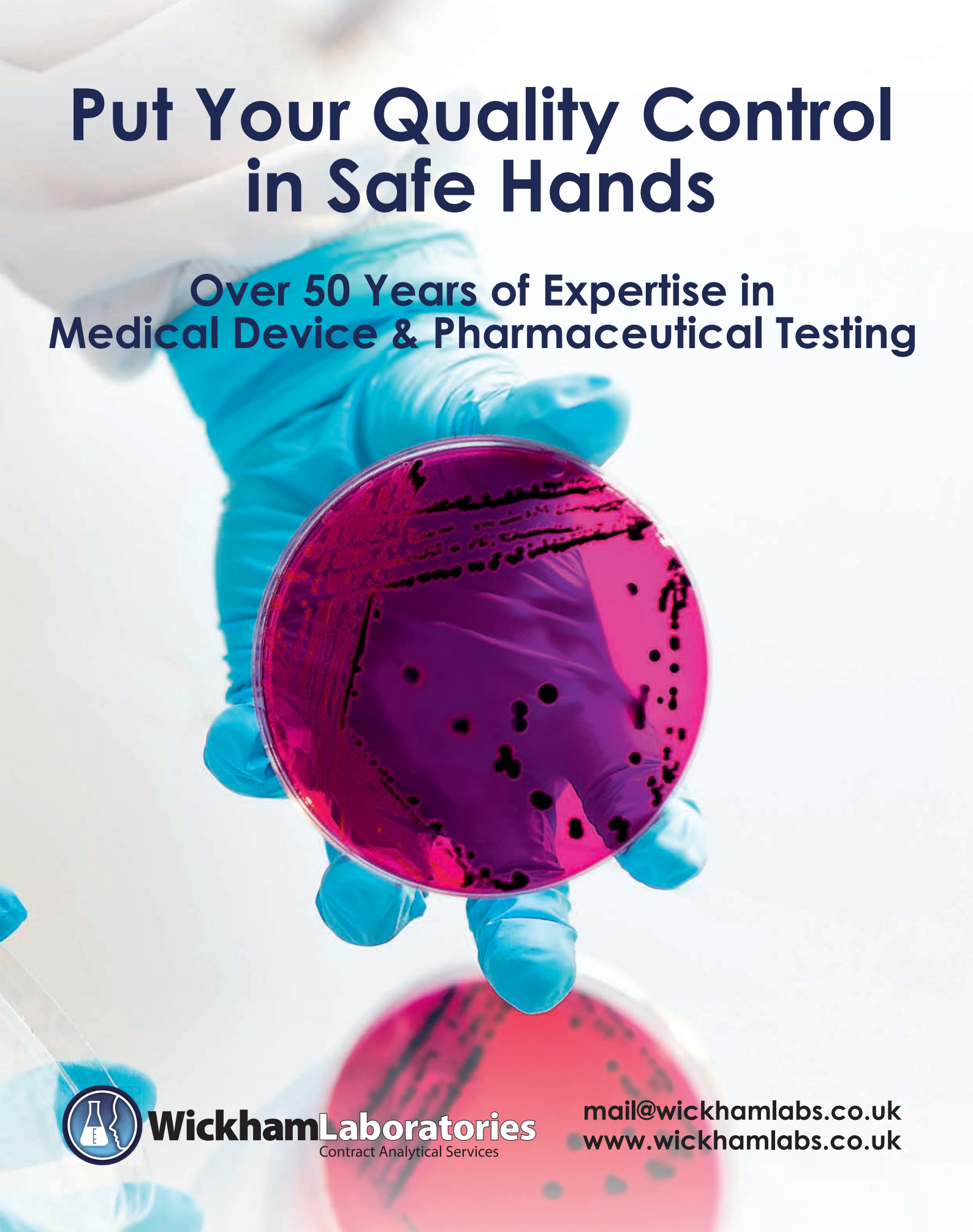

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Search and Destroy

Serialization will certainly help in the battle against counterfeiters, but there are other steps that manufacturers can take.

By Ioannis Manolopoulos

According to the International Anti-Counterfeiting Coalition, the illicit market of counterfeit drugs has a global value of more than one trillion Euros – and consultancies in Europe estimate that this may grow to more than two trillion Euros by 2020 (1). Globalization has created the ideal conditions for the counterfeit drug industry to boom, with sales made easier through lower transportation costs and little or no marketing costs for counterfeiters in comparison to legitimate pharmaceutical businesses. Countries that lack effective drug regulatory agencies are seen as particularly easy targets by counterfeiters, but counterfeit medicines have also slipped into legitimate supply chains in Europe and the US too. Some pharma companies have retaliated with well-thought out strategies that involve strong investments in anti-counterfeiting technologies (both overt and covert) and awareness campaigns that educate consumers on how to spot counterfeit medicines – and how to report them – as well as how to buy medicines safely online. Many big pharma companies have dedicated anti-counterfeiting teams, but small and medium enterprises are often much less likely to respond to the dangers because of a lack of resources.

Action against counterfeits from regulators and authorities, although potentially highly effective in some ways, has also served to constrain genuine supply chains through measures that are not unified and that lead to the need for new, complex (and expensive) systems. Both the EU and the US have implemented legislation around serialization, but the two systems are quite different. The US' Drug Supply Chain Security Act (DSCSA) is being rolled out in different phases (the final phase is slated for 2023), whereas the final deadline for the EU's Falsified Medicines Directive (FMD) is February 2019. Both systems require slightly different information and give no guidance on what serial number systems or data collection systems should be used. Companies have been forced to expend significant resources on dissecting the new regulations and implementing appropriate solutions – and there are huge concerns about how ready the industry is for the impending deadlines. Industry surveys show that only 51 percent of pharmaceutical manufacturers are expected to be ready to provide serialized products by the deadlines outlined within serialization regulations (2); in the EU, many member states won't even have a national system in place by the February 2019 deadline for providing the information. Under the FMD, an "EU hub" will collate the serial data of drug products from across the EU, but each country will also require a national hub that will allow local pharmacies in each country to verify a dispensed product against national records. To date, only nine EU countries have their National Medicines Verification Organization (NMVO) ready (2).

Dealing with data

Despite the challenges, every company – whether large or small – has a duty to help deter counterfeiters. On a company level, the ability of pharma manufacturers and repackaging organizations to provide large volumes of serialization data within different countries is highly variable. One of the main hurdles for companies is simply identifying the right technological serialization systems. Drug manufacturers have been working with machine and software vendors for years to conduct research and evaluate the most efficient solutions, such as whether to opt for integrated solutions from one supplier, or systems that can coordinate, as painlessly as possible, existing production and logistical processes. When it comes to serialization and information management, there are five levels:

- Level 5: the highest possible level used for governmental reporting systems
- Level 4: corporate IT solutions that manage serialization and business processes – often referred to as the enterprise level.
- Level 3: localized systems within the manufacturing plant or distribution center
- Levels 1 and 2: inputs and line controllers into the level 3 servers and file systems, including vision controllers and packaging machinery.

For pharma companies, Level 4 is often considered the most vital element of the data lifecycle, as it includes the collection, management and verification of serialization data. It is the level where the big data lifecycle starts the journey to/from authorities and to/from wholesalers/manufacturers, and the system must manage manufacturing, packaging, warehousing and distribution. Large Level 4 software developers tend not to be amenable to sharing their proprietary software, so manufacturers must choose between two solutions: either serialize on their own with a custom solution, or use a cloud-based solution. Companies tend to be split between using cloud-based or hardware storage. Neither choice is necessarily "better" than the other, but it is important to judge which works best for your individual circumstances.

The Numbers Speak for Themselves

Counterfeit and falsified drugs are one of the most pressing global public health crises of the twenty first century. Counterfeit drugs may be contaminated, be in the wrong dose, or contain the wrong or no active ingredient – counterfeit drugs have been found to contain rat poison, brick dust and arsenic. The rigor of legal control within a country often affects how easily counterfeit medicines can be distributed, which is why they are most prevalent in certain geographic areas.

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1 in 10

medical products in low- and middle-income countries is substandard or falsified.

116,000

additional deaths from malaria could be caused each year by "bad" antimalarials in sub-Saharan Africa

ONLY 20%

of WHO member states have effective drug regulation systems in place

$14 million

worth of potentially dangerous pharmaceuticals seized in Operation Pangea XI. 3,671 web links selling illicit pharmaceuticals closed down

52.8%

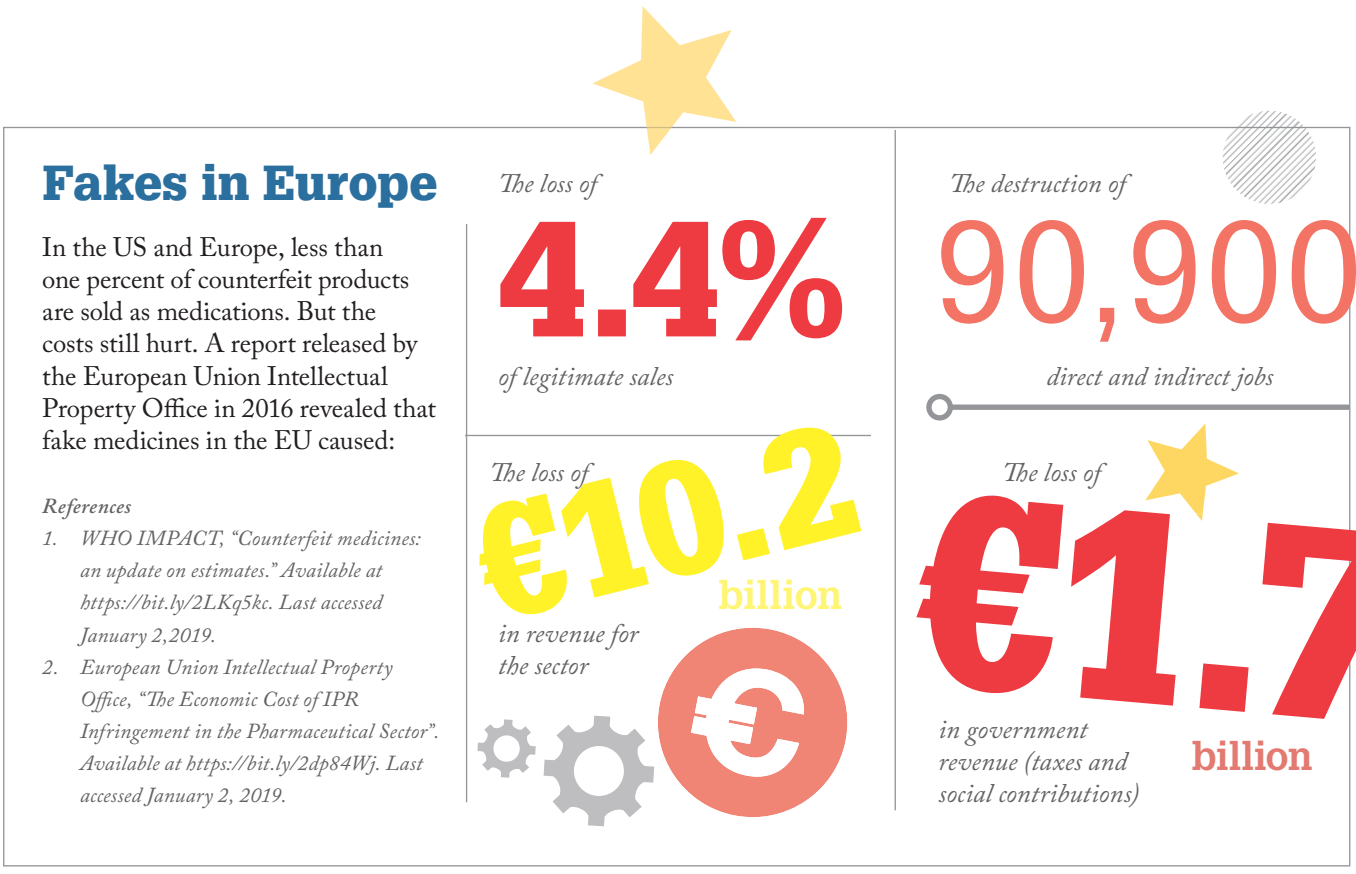
of counterfeit medicines found in legitimate supply chains are for life-saving treatments

Every region of the world experienced an increase in pharmaceutical crime incidents in **2017**

Despite the apparent conundrum of choosing the right system, it's worth noting that the main software products available on the market for serialization, in general, do not vary greatly in function.

In the early days of serialization, initial discussions focused on the need for "aggregation," where a shipper needed to provide 100 percent accurate linking of the serial codes within each case to the serial code of the case itself. This seems to have been refined based on practicality and, from an economic standpoint, most companies have agreed that aggregation makes sense to be placed on the packaging line. Large shipping units, such as pallets or big boxes and bags are far easier to scan as a single unit and for their codes be introduced to enterprise resource planning (ERP) systems. Without aggregation, it would be necessary to scan every item individually on a pallet, which could be more than 10,000 units.

More recently, industry attention is moving to what takes place at third-party logistics providers (3PLs), as these are generally seen to be potentially exploitable points in the supply chain because of their lower levels of GMP. Some manufacturers have also realized that the optimal point for aggregation may be in the warehouse, as orders are put together for shipment there, rather than at the end of a packaging line. The main challenge of moving aggregation to this step is that manufacturers usually have no distribution agreements with



secondary wholesalers. In addition, some wholesalers may work with non-pharmaceutical products, and their staff may not have any specialized knowledge or experience in pharmaceutical warehousing or the quality assurance management of serialized products. The consequences of not having dedicated staff at this stage of the supply chain can be disastrous for companies that do not apply aggregation (aggregated batch sizes require less man hours). I believe that both the EMA and FDA have recognized the importance of manual labor and shop floor activities, and will be looking towards building up strong quality assurance systems within warehouses and supply chain departments.

Beyond barcodes

Serialization is not enough to crack the counterfeit nut, but there are also a wide variety of other solutions that can help deter counterfeits, such as specialized cartons, labels, overwrapping, tamper-evident tape, holograms, and color-shifting images – and even on-dose identifiers, which mark individual tablets. Tamper-evident packaging has been flagged by many companies as a dependable method of slowing the movements of the counterfeit industry, enabling fake products to be intercepted and verifying the authenticity of products to end-users (4).

Today, many consumers will knowingly buy counterfeit products, such as fashion accessories and clothes, but counterfeit medicines pose serious health risks. The true extent of the problem is unknown, and despite efforts to make counterfeiting more difficult, those involved in the practice have evolved their methodologies. Serialization and track-and-trace technologies promise to help manufacturers fight counterfeits by providing more traceability than ever before over medicines in the supply chain. But we can't stop there. Companies must not be complacent and must also continue to invest in new solutions. The way to beat the counterfeiters ultimately lies in making tampering and counterfeiting more challenging and less profitable.

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Back to Nature

It's time for pharma manufacturing to leave behind the highly energy-dependent and inflexible processes of the 20th century and embrace more sustainable and efficient biological approaches. Let's "biologicalize" manufacturing.

By Bill Whitford

Pharma is undergoing an age of transformation, and by that I mean not just in terms of business models and arguments around pricing, but also manufacturing. The digitalization of manufacturing with "Industry 4.0" is changing the way we think about making drugs, with technologies such as artificial intelligence and continuous manufacturing being intently discussed. But there are also fascinating advances in biology leading to a new transformation that some are calling the biologicalization of manufacturing.

Biologicalization in manufacturing has been defined as, "the use and integration of biological and bio-inspired principles, materials, functions, structures and resources for intelligent and sustainable manufacturing technologies and systems with the aim of achieving their full potential" (1). Bio-inspired chemistries, surfaces and systems have impacted many areas of the global economy, including materials, operational technologies, manufacturing processes and final products.

Manufacturing in the 20th century was – and to a large extent still is – characterized by the use of toxic materials as organic solvents or heavy metals for process chemistries. It often employs dedicated manufacturing facilities and reactors exhibiting process inefficiencies and undesired byproducts and waste. The integration of natural and biological principles could result in more sustainable and resource-efficient manufacturing approaches, and more environmentally friendly and energy-efficient products.

Nothing new, yet brand new

Making use of biological reactions is not new – the ancient Egyptians used to convert grain sugars to alcohol when making beer, and brewing still uses biological reactions today. But recent advances in systems and synthetic biology have made it possible to precisely engineer microorganisms to perform more useful and efficient functions. In just one example approach, scientists have genetically engineered classic bacterial and yeast platforms to produce products such as gasoline and polyesters. Many different types of organisms can be considered miniature factories, and the next generation of synthetic biology promises even more pharmaceutically-relevant applications. The genes encoding catabolic or processing functions are being re-engineered to provide entirely new pathways to produce the desired (unnatural) products, for example. Through this, and the careful selection of the appropriate host cell or organism, novel and bioactive molecules can be produced without the need for harsh reaction conditions or environmentally dangerous chemicals.

Biologicalization has also been applied to small-molecule pharma. Examples here include a novel crystallization induced dynamic resolution-based aprepitant synthesis, which eliminates over 80 percent of water, raw materials and waste; the Diels-Alder reaction, providing 100 percent atom economy (2); and a catalytic method of ibuprofen synthesis that nearly doubles atom efficiency and eliminates significant amounts of metal catalyst waste.

Another example can be found in the production of the popular drug Lipitor. Pfizer reduced the organic waste produced in its synthesis by 65 percent by changing the manufacturing process to include a palladium-catalyzed cross-coupling reaction. But the remaining 35 percent, consisting largely of the organic solvents methanol and tetrahydrofuran, is still significant, adding to the waste streams associated with this process. Bruce Lipshutz, an organic chemist with the University of California, Santa Barbara, is devising sustainable manufacturing solutions to problems associated with our non-sustainable 19th century methods, by working in ways that follow nature's lead. For example, he and his co-workers have developed a system, using water as the reaction medium, that allows for many common reactions, including cross-couplings, to occur at room temperature and with only parts per million of transition metal catalysts, and especially, palladium. This system consists of an amphiphilic surfactant that will self-assemble in water to form micelles, within which the catalysis takes place, thereby avoiding traditional uses

of organic solvents. This biomimetic super-structuring of the reaction provides many benefits, including reduction of environmentally problematic materials typically required.

A central problem with using biological approaches at manufacturing scale is that they are often slow, inefficient and unstable since they are living systems. But this is improving with the integration of bio-inspired tools with modern "digital" and automated manufacturing schemes. This includes cloud-based data techniques, machine learning, AI and autonomation. Application of the industrial internet of things (IIoT) and model-based control is also changing the face of modern manufacturing. Harmonization of digital manufacturing principles with structures and chemistries from biological systems may define the next generation of manufacturing technology and systems.

Klaus Schwab, founder and executive chairman of the World Economic Forum Geneva, famously put it, "the digital revolution […] is characterized by a fusion of technologies that is blurring the lines between the physical, digital, and biological spheres" (3). This transformation will involve sustainable materials and manufacturing processes, resource-efficient products and services, as well as new medical treatments based on the application of both biological mechanisms and 4.0 digital approaches. For example, labile protein biologicals such as Cerezyme and Fabrazyme have, for decades, been produced in perfusion bioreactors culturing animal cells. However, the industry has tended to avoid such procedures because of the lack of efficiency and control required for large-scale biopharmaceutical manufacturing. Today, advances in in-line monitoring, multiplexed analytics and model-based control are providing robust and intensified perfusion processes that are taking over the industry.

We all know cells in our body use

enzymes to catalyze the reactions required for life. These enzymes are now being repurposed to produce useful compounds that are difficult, expensive or employ problematic chemicals to make using traditional chemical synthesis methods. Researchers are already stringing together in-vitro enzyme reactions to produce pharmaceutical entities through more environmentally friendly reactions.

Integral to the development and application of these principles is progress in our understanding of biological systems. One of 2018's Nobel Prize in Chemistry winners was Frances H. Arnold, Professor at the California Institute of Technology, who invented systems for the directed evolution of enzymes, which is now routinely used in the development of tools such as catalysts in manufacturing. This technology also supports other 4.0 goals, such as the environmentally friendly manufacture of renewable fuels and pharmaceuticals (4).

Many highly synthetic and energy demanding manufacturing processes used today actually have biological origins. The observation that wine turns to vinegar led to the so-called German Method of acetic acid manufacturing. Here, an alcohol-containing feed (created by natural fermentation) is percolated through a tower packed with wood shavings seeded with Acetobacter. This process supported the sequential aerobic fermentation of the alcohol by the bacterium, allowing the collection of a solution of acetic acid at the bottom. This was considered a modern and efficient process until it was discovered that it could be generated synthetically. The first published synthetic acetic acid reaction sequence consisted of chlorination of carbon disulfide to carbon tetrachloride, followed by pyrolysis to tetrachloroethylene and then aqueous chlorination to trichloroacetic acid – finally concluding with an electrolytic reduction to acetic acid. Such first-generation highly synthetic and unnatural manufacturing methods, while more productive than the original, are what have led us to the 20th century style of manufacturing that we now understand to be rather unsustainable.

Embracing sustainability

Today we are seeing the biologicalization of the process through many approaches, including the engineering of bacteria to express high levels of new alcohol dehydrogenases – enzymes instrumental in the conversion of ethanal to acetic acid. Such genetic and metabolomic engineering,

as well as digital manufacturing-based advances in fermentation technologies, are making acetic acid manufacturing more sustainable, including lower manufacturing energy requirements and the possibility of employing low-cost carbohydrate sources as organic wastes and agricultural residues.

Such approaches also exist for the manufacture of protein, biological and cell therapy products. For example, manufacturing of oligonucleotides for antisense, aptamer and siRNA-based therapeutics previously evolved using solid-phase techniques. Yet, the Caruthers' phosphoramidite chemistry upon which it is based requires a number of toxic and difficult solvents – and has remained largely unchanged for over 30 years. But solutions employing more water and fewer organic solvents and metal catalysts are becoming more widespread. One illustration of this progress is that acetonitrile and methanol are still popular solvents in much chromatography, but they suffer from several drawbacks from an environmental point of view. Alternative, greener mobile phases employing *a*-cyclodextrins as additives produces a remarkable increase in water compliment for the mobile phases, without loss in the resolution or efficiency of the separations. It's important to note that the cyclodextrins themselves are prepared by enzymatic treatments of simple starch: commonly, cyclodextrin glycosyltransferase and *a*-amylase.

The manufacturing of RNA vectors, a key component of mRNA-based gene therapy, yields a story similar to acetic acid history. The old cell-based "natural" approach to manufacture yielded a relatively low mRNA yield and required purification from a multitude of contaminants. Newer polymer chemistry-based approaches worked well, but these methods often came with negative characteristics associated with highly synthetic chemistries. For these reasons, we now see bio-inspired, but cell-free aqueous liquid-phase methods most commonly employed. DNA-template directed polymerase (enzyme)-led transcription processes are very efficient and much more sustainable approaches (5).

"Integration of natural and biological principles could result in more sustainable and resource–efficient manufacturing."

Illustrating the increased interest in the field, Fraunhofer-Gesellschaft (based in Berlin) sponsored a meeting last June on current initiatives to replace many of pharma's highly artificial and manual manufacturing approaches with more biomimetic and digitally directed procedures and chemistries (6). This meeting, The Biological Transformation of Manufacturing, brought together experts from around the world to discuss both goals and mechanisms for supporting the increased use of this biotechnology for sustainable growth and innovation. There, we heard pharma-relevant lectures from speakers such as Thomas Schmitz-Rode, Director, Helmholtz Institute of Applied Medical Engineering, RWTH Aachen University, who has developed his thesis on how "control of biological uncertainty in the production process is the key to quality-assured, individualized cellular therapy…" While there have been movements to "go back to nature" for decades (and this is a very prominent trend amongst consumers today), manufacturers today are focusing more on manufacturing efficiency, bio-integrated but novel technologies, empowered by modern digital and nano-techniques.

Whatever the specific chemistries, technologies or applications – "biologicalization" promises to change our concept of manufacturing. Leaving behind the old 20th century concept of highly energy-dependent, inflexible and dangerous chemical-employing processes, and embracing more efficient and biomimetic procedures employing water-based and sustainable chemistries, will enable us to better support our societies in the coming century.

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Process Intensification: Getting More From Less

Intensifying or simplifying your bioprocess can mean more product, shorter manufacturing times, or lower costs – understanding what matters most is key to making the right decisions.

By Serena Fries Smith

It's no secret that the biopharmaceutical industry is under intense pressure to reduce costs – especially in manufacturing – and getting more output from a given process is a clear win. Process intensification does just that. It can take an existing process and optimize it to increase output: more product in a shorter time, with fewer steps, and from a smaller working footprint. Process simplification, on the other hand, focuses on streamlining activities to increase efficiencies.

Which option is best: intensification or simplification? It ultimately depends on the type of molecule you're making, the current manufacturing challenges and bottlenecks you're facing, and the stage of development your product is in. Process changes can occur at any stage during development, even post-launch, and the better characterized your existing process and product are, the easier it will be to evaluate the impact to the critical quality attributes of your product and implement changes (1).

Evaluating impact

During early-stage development, there's usually pressure to quickly identify a first-generation process and get the molecule into the clinic as quickly as possible. After this point, there is typically time to consider where opportunities for process intensification and simplification exist. These pre-launch changes are driven by commercial requirements – can I effectively and efficiently manufacture enough material to meet patient demand? And manufacturing needs – is this process robust enough to run consistently for the lifetime of the product?

During late-stage development, there may be pressure to minimize changes and focus on finalizing the commercial process to prepare for launch. But while late-stage and post-launch process changes can be more difficult to implement, they should still be considered when there are opportunities to reduce risk of manufacturing failures, increase throughput, and improve the consistency of the product and process. Regardless of where you are in the lifecycle of your molecule, there will be no shortage of potential opportunities for improvement. The key is determining which ones to pursue:

- Should I streamline?
  To streamline a process is to reduce unnecessary steps or operations. Focusing on these areas of improvement could reduce processing time and the risk of manufacturing and contamination failures. One common area that can usually be streamlined is cell expansion. It may be possible to reduce the number of expansion steps in the process, or reduce the amount of aseptic manipulations required during cell expansion. Another area to consider would be release testing. With current advancements in analytics, it is possible to replace cell-based assays, which take weeks, with significantly shorter assays.

- How do I intensify?
  Process intensification enables you to get more out of your process. For an upstream process, you could consider transitioning from fed-batch to perfusion, or implementing a hybrid, high cell density process enabling you to increase the amount of protein produced without increasing batch size or processing time. For a downstream process, you could optimize chromatography resins to improve cycle times and increase yields. All of these changes would result in an increase in material throughput.

- Could this be simplified?
  Identifying tasks that are labor or time intensive, and simplifying those operations enables you to focus resources on more critical activities. Some areas to consider are media and buffer preparation, as well as material handling and transfer. There are likely opportunities to outsource or automate these tasks.

Before making any change in a manufacturing process for a biologic however, it's important to understand the impact of the change on the molecule as well as the business. First, the change must not affect the safety or efficacy of the molecule being produced. And second, the change should have a positive effect on the manufacturability of the molecule. Depending on the process and how well it is understood, demonstrating that there is no impact to the molecule is sometimes the most challenging part of implementing a change. For this reason, you may feel that it is better to continue with your existing process, especially post-launch. I believe it is important to look at each situation independently prior to determining if the reward is worth the effort.

Improving manufacturability

Overall manufacturability is a key consideration to whether or not a product will be commercialized. Process simplification or intensification could greatly improve the manufacturability of the molecule through improved robustness, increased throughout, reduced supply concerns, or reduced cost of goods. These activities have the potential to make a bad process good or a good process great. (2).

Process intensification is used to get more out of the process, whether it's by producing more product upstream, or retaining more product downstream. Intensifying the process requires changes in manufacturing – different media or resins, new operating ranges, or even replacing specific unit ops, and therefore has the potential to have the greatest impact on the molecule. For this reason, these activities are typically done during early phase development. They can still be pursued during late-stage development or even post-launch, but you would first need to demonstrate no adverse effect on the identity, quality, purity, and potency of the biological product.

One area where process intensification may be critical is in the rare disease space. The majority of biological products in development for the treatment of rare diseases are not the more common monoclonal antibodies, but rather are enzymes, fusion proteins, and cell therapies. These products are typically more challenging, and therefore more costly, to manufacture, which makes process intensification crucial to successfully bringing these products to market.

"We are exploring opportunities to use more efficient purification technologies to reduce the number of purification operations required to generate purified drug substance. Our ability to simplify processes improves likelihood for successfully validation, reduced scope of process development and characterization, reduced number of manufacturing deviations and failed manufacturing campaigns, and improved yield."– Andrew Keefe, Principal Development Engineer at Shire.

Process simplification can also have significant positive impacts on manufacturability, and most simplifying operations are likely to have no impact on the molecule, and are, therefore, routinely implemented even post-launch.

Analytical testing is an area where simplification can improve the release of biological products. For all sterile products, sterility testing is required for release and may be the longest test to complete. This is a challenge for all of those molecules, but for cell therapy products it is even more of a concern. Monoclonal antibodies, for example, are targeted to specific diseases and, once purified, are typically stable for multiple years. Cell therapies, on the other hand, are live cells and may be patient specific. Therefore it is imperative that the material gets to the patient without delay, and identifying viable solutions to streamline analytical testing is crucial to getting those products to the patients that need them.

"Microbial testing is required at different points throughout a manufacturing process, but standard methods take too long to be useful for cell therapy products. USP mycoplasma testing takes 28 days; Vericel's method has reduced that to about six hours [with the] MycoSEQ™ mycoplasma detection assay."– John Duguid, Ph.D, Senior Director of R&D at Vericel Corporation (3).

Conclusion

Simplifying or intensifying a process may make the difference in whether or not a company can manufacture or even launch a successful biologic. Choosing what and when to intensify can be difficult. With any change, the benefits must always be carefully weighed against the potential risks. But understanding your rationale for change, conducting thorough reviews of the impact to the product and process, and leveraging the expertise of a trusted partner, can lead to tremendous success and result in more product at better costs by transitioning your bioprocess from good to great. A former colleague of mine who worked in the CMC group would say, "Keep the patient first when evaluating product and/or quality risks." For all situations, the patients' best interests should be top of mind when you are making these assessments.

Serena Smith is Director of Strategic Customer Engagements at Thermo Fisher Scientific, and a bioprocessing leader with over 17 years of industry experience.

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Pharma in the Firing Line

The 2018 Congressional midterm elections are over: the US is back to divided government. And with Democrats controlling the House, and Republicans expanding their majority in the Senate, the US pharma industry could be the number one target for politicians.

By George Chressanthis and Charlie Thompson

The pharma industry has long been targeted for political discussion by critics, but this was raised to a new level when both the Democrats and Donald Trump put the industry in their crosshairs during the 2016 presidential election. Both Hillary Clinton and Bernie Sanders took aim at the industry during their debates. Clinton noted in a Democratic town hall discussion that drug companies were on her most proud enemies list, along with the National Rifle Association, health insurance companies, the Iranians, and Republicans. President-elect Trump then attacked the pharma industry on its pricing practices, with this now famous comment during his pre-inaugural news conference: "And the other thing we have to do is create new bidding procedures for the drug industry, because they're getting away with murder."

Trump's concern over drug pricing mirrors results from a March 2018 national tracking poll in the US (1). This poll found "passing legislation to bring down the price of prescription drugs" received the highest percentage of a top priority issue at 52 percent. The same poll found 80 percent of people saying the cost of prescription drugs is unreasonable and felt not enough is being done to bring costs down (Congressional Republicans [83 percent] and Democrats [82 percent], and President Trump and his administration [77 percent]). People view Congress and the White House as being equally culpable in not doing enough to address the high cost of prescription drugs.

Of course, the 2018 Congressional midterm elections are now over. And after a bitter political fight, the US is back to divided government, with Democrats controlling the House, and Republicans slightly expanding their majority in the Senate. The big question is what follows next: bipartisan collaboration or political conflict and policy immobilism?

Prescription drug prices, infrastructure, and immigration are three areas often noted in the press as possible common areas for working together to pass meaningful legislation. This sentiment of desired collaboration mirrors a post-midterm election survey finding where 68 percent of likely voters wanted to see House Democrats focus on areas they can work with Senate Republicans and President Trump (2). Voters believe that reducing the cost of prescription drugs has the best chance of bipartisan action than other previously noted issues (see sidebar: "Can't we all just get along?" for why collaboration in other areas is less likely).

Why? First, both Democrats and President Trump have been highly critical of pricing practices by the industry. Second, reducing the high cost of prescription drugs is an issue that wins voters, especially the elderly – a critical demographic voting-block in elections. People 65 years and older have the highest volume of prescriptions than any other age group, and overall prescription growth has been driven by an increase in elderly population. As previously stated, Democrats were effective in pushing healthcare as a key difference between them and Republicans. Republicans desire to counter this notion by showing their efforts to reduce drug prices.

"First, both Democrats and President Trump have been highly critical of pricing practices by the industry. Second, reducing the high cost of prescription drugs is an issue that wins voters, especially the elderly."

Third, President Trump and his administration activities, by the Department of Health and Human Services (HHS) through Secretary Alex Azar, and the FDA through Commissioner Scott Gottlieb, realize the political benefits of attacking high drug prices and have already pursued numerous avenues to lower them:

- The Trump administration rolled out its American Patients First blueprint to lower drug prices and reduce out-of-pocket costs in May 2018. The blueprint covers many areas to reduce drug prices, including focusing reforms on the opaque world of pharma rebates

Our Preferred Approach

There are a number of policy approaches that we think could reduce drug prices, while preserving the incentives needed for drug innovation:

- Increasing all forms of competition.
- Opening the opaque system of rebates and discounts received by PBMs.
- Ensuring those price concessions are given back to patients.
- Increasing the speed of reviewing of drugs (without forsaking quality and safety).
- Improving efficiencies in the overall supply chain.
- Enacting public policies to facilitate increasing the productivity of R&D pipelines.

The last point is critical since while recent years have seen an increase in the launch of new specialty medicines (especially biologics), prior empirical evidence has shown increasing inherent risks and probabilities of failure per stage of development, across major therapy areas, and from each stage to launch (1). Plus, previous evidence has shown the greatest risks to lower R&D productivity are probabilities of failure from passing phase III and II clinical trials (2). Lastly, a large-scale pharma R&D productivity study found that differences in organizations (e.g., large versus small pharma companies) led to varying pipeline results (3). Specifically, larger companies (as noted by sales) tended to halt clinical trials later in the process, resulting in significantly higher opportunity costs.

Furthermore, the government can help pharma companies mitigate these greater R&D risks and costs by pursuing the following policies:

- Enacting favorable tax policies to encourage development in certain therapy areas (like it did with the Orphan Drug Act).
- Passing exemptions in anti-trust provisions to encourage data sharing of clinical data between companies to determine which R&D avenues should continue versus shut down.
- Developing special tax incentives for specific capital equipment needed for more effective identification of potential targets of projects in discovery and pre-clinical for further research.
- Investing more money for basic research through governmental agencies like the National Institutes of Health and encouraging the dynamic collaboration between academia, research foundations, venture capital companies, pharma organizations as seen in the US.
- Protecting the intellectual property of patents that are necessary to reward companies for their risk-taking.

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and discounts (3).

- President Trump has jawboned pharmaceutical CEOs to limit and/or delay their company price increases as he did with Pfizer and Novartis (4). Pfizer recently reported pricing pressures, from many sources, including those from the administration (5).
- The Biosimilar Action Plan announced by the FDA in July 2018 was rolled out to lower drug prices through promoting greater competition by increasing the availability of biosimilars in the US (6). FDA Commissioner Scott Gottlieb has been critical of industry attempts to limit biosimilar competition through the patent system and biologics are among the most expensive medicines, representing a meaningful portion of total US drug spending.
- The FDA has accelerated the approval of generics, a favored policy approach by Commissioner Scott Gottlieb, resulting in substantial savings estimated at $26 billion by the administration's Council of Economic Advisers in October 2018 (7). In fact, over 90 percent of dispensed prescriptions in the US are now generic (8).
- President Trump signed, in October 2018, two bills that passed virtually unanimously by Congress to ban "gag orders" in contracts between pharmacies and

insurance companies/pharmacy benefit managers (PBMs) to tell consumers that they could get drugs at a cheaper price by paying cash rather than the negotiated contract price on their drug plan (9).

- In a controversial move in late October 2018, President Trump announced a five-year experiment to lower Medicare Part B drug prices. Administered by the Centers for Medicare & Medicaid Services (CMS), US prices will be linked to what countries with similar economic conditions pay for drugs by creating an International Price Index (IPI) Model (10). Not surprisingly, the Pharmaceutical Research and Manufacturers of America (PhRMA) forcefully criticized this Trump policy as essentially imposing foreign price controls from other countries that threaten to reduce innovation and could be detrimental to patients. Similar criticisms have been levied by pharma CEOs, The Wall Street Journal, and James Greenwood, President and CEO of the Biotechnology Innovation Organization (BIO). Equally unsurprisingly, consumer groups like the AARP favor the policy approach and want to extend price restraints on Medicare Part D drug costs.

Fourth, attacks on the drug industry and the use of price controls are possible due to the breaking down of a traditional coalition of pharma manufacturers, health plans/PBMs, and Republicans (with silent supportive partners being business, hospitals and physicians) that has protected the US pharma industry from such direct threats over the years (11). President Trump is not a traditional Republican, and his direct approach of erecting price controls aligns with his populist philosophy and wanting to "get things done." The public has also shifted their views, the majority now wanting caps on prices charged by hospitals and physicians. Businesses are also concerned about the rising cost of providing healthcare to their employees. Thus, there is an opportunity for President Trump and Congressional Republicans who wish to fend off healthcare as a negative issue, and Democrats to align on this issue.

Fifth, unlike other issues discussed as possible areas for collaboration, reducing drug prices increases drug adherence, improves health and economic outcomes, and reduces overall healthcare spending administered through federal programs. Also, such initiatives can be done without Congressional approval, and ironically, can be done via provisions within the Affordable Care Act (ACA), something President Trump and Republicans have aggressively worked to repeal. Finally, such an approach by the President and fellow Republicans provide an excellent position to campaign on for the 2020 presidential and congressional elections, countering healthcare issues the Democrats effectively levied during the 2018 midterms.

Given all the above reasons and efforts already underway to tackle drug prices, what more can be done to reduce drug prices?

The bipartisan policies on the horizon

There are a number of bipartisan policies that could be taken to reduce Medicare Part D prices that are different from policies already in place. For example, the federal government could use its bargaining power to negotiate directly with plans on the drug prices for Medicare Part D recipients. This approach has been previously advocated by candidate Trump and liked by Democrats. This approach would require the government to take on the role, now currently done by PBMs under contract, to negotiate drug prices for Medicare Part D. This would require a redoing of a 2003 law preventing the government from interfering in these negotiations. President Trump recanted this approach back in May 2018, but the political winds could change his thinking.

Another approach would involve the federal government establishing a pricing scheme for drugs under Medicare Part D that is similar for drugs for Medicaid recipients. The reimbursed price would be based on a formula using the average manufacturer

"The fear is that President Trump, given his rhetoric, desire to negotiate deals, and populist philosophy, will succumb to a more direct price control option."

price (AMP), best price per unit (or best commercial price), plus further technical adjustments, with a significant discount then applied to the calculated price (12). This approach requires no negotiations – simply a calculation. The question simply becomes the discount rate applied to this Medicaid-like formula price for Medicare Part D recipients.

A similar approach to the recent experiment enacted for Medicare Part B pricing by leveraging the creation of an international pricing index could also be undertaken. This would, in effect, expand importing foreign price controls onto the structure of US drug prices.

Finally, a direct price control level (using health and economic outcomes, and cost-effectiveness data) could be established as well as a referencing pricing scheme, as employed in France. The government would establish the reference price (without negotiations), and where requests by pharma companies for premium prices above the reference level must be supported through a demonstration of evidence showing greater value.

All of the above potential broad bipartisan policy approaches impose some kind of price control scheme. Traditional microeconomic theory and practice suggests that such price controls would result in lower drug R&D, less diffusion on new drug technologies, lower health outcomes, and higher healthcare spending (13). If a policy approach is to be chosen among the above options, the least onerous would likely be if the federal government established a Medicaid-like pricing scheme for drugs under Medicare Part D, because of its simplicity and smaller ad hoc governmental decision footprint. But the fear is that President Trump, given his rhetoric, desire to negotiate deals, and populist philosophy,

Big Pharma Responds

On January 11, 2017, Donald Trump, then President-elect, sent pharma stocks tumbling when he said: "And the other thing we have to do is create new bidding procedures for the drug industry, because they're getting away with murder." But how did Big-Pharma CEOs respond?

"One way of lowering health-care costs is to have more innovation and more competition."
Ian Read, Chairman and CEO of Pfizer

"Industry has to price in an empathetic way. Just because you can demonstrate value doesn't mean it is affordable."
Andrew Witty, CEO of GlaxoSmithKline

"The new administration has been pretty vocal about supporting innovation. They understand that when you spend money on research and you develop intellectual property there needs to be some level of return for that investment."
Joe Jimenez, CEO of Novartis

"If you provide true medical differentiation coupled with a strong intellectual property position, I think the US will continue to reward this kind of innovation. If you don't offer that then, frankly, I think it is the right thing that prices should come down."
Severin Schwan, CEO of Roche

"Pricing will remain a challenging issue for those of us who are in the research-based pharmaceutical industry, as well as a challenge for the overall healthcare system in terms of what it can afford."
Ken Frazier, Chairman and CEO of Merck

"It's very difficult to understand what all those comments and tweets will end up being."
Olivier Brandicourt, CEO of Sanofi

"Pharma companies are in a difficult position, and admittedly, one mostly of their own making, and thanks to irrational price increases, especially from bad industry actors."

will succumb to a more direct price control option. This would not only be counterproductive for the industry but could also create adverse effects for patients.

What should pharma companies do?

Pharma companies are in a difficult position, and admittedly, one mostly of their own making, and thanks to irrational price increases, especially from bad industry actors. But it would be wrong to think that maintaining the present course or ignoring the problem are the correct strategic paths forward. It would also be wrong to assume that President Trump is the cause of this dilemma.

The industry's shift to specialty medicines requires revolutionary thinking, new strategic and tactical approaches, and the adoption of novel analytics and data needed to support a framework to commercialize successfully these drugs. Specific business policy steps need to be taken by pharma companies, with some starting immediately, while others adopted and taking effect over the longer-term:

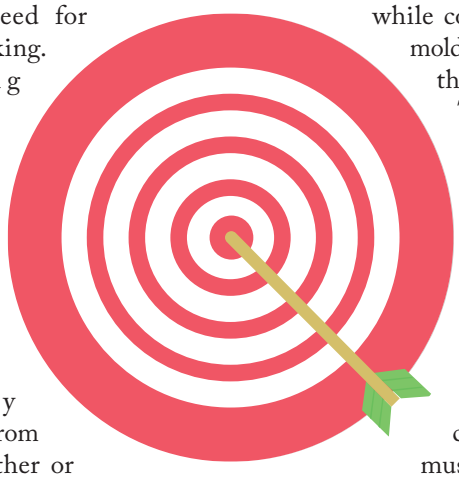
- Alter the objective of what pharma companies actually sell, not medicines, but healthcare outcomes, such as improvements in health and economic outcomes, quality of life for both patients and caregivers, worker productivity, etc.
- Use industry associations, such as PhRMA and BIO, to apply peer pressure to industry players that indiscriminately raise drug prices, threaten the public trust, and damage the industry's reputation.
- Shift away from a volume-based to value-based commercial model design (CMD) and be more patient focused.
- Integrate analytics used in health economics and outcomes research (HEOR)/real world evidence (RWE) with those methods used in traditional commercial operations.
- Think ahead by designing clinical trials that can be more quickly commercialized pre- and post-launch.
- Learn how to support analytically payer-performance based contracts.
- Leverage a greater variety of data to support a value-based CMD, such as patient-level claims and electronic health records, wearable data, and data generated through digital channels and social media. This also means knowing how to link newer and traditional datasets.
- Adopt artificial intelligence and machine learning technologies applying analytical methods for real-time insights, predictive modeling, simulation, and next-best option decision-making.
- Rethink salesforce strategic design and outcomes (size, structure, allocation, physician-disruption and scenario planning). This means a shift to smaller and highly trained sales forces on the science/clinical/medical aspects of more complex specialty medicines.
- Move away from a primary detail equivalent (PDE) sales force allocation model to one that focuses on the delivery of disseminating scientific information designed ultimately to affect outcomes. Value-based "informative" messaging will be more critical over frequency-based "persuasive" PDE allocation models.
- Focus more on direct-to-patient (DTP) over direct-to-consumer (DTC) advertising, and/or dramatically alter the approach of current DTC advertising for specialty medicines to be more value-oriented.
- Develop sales operations such as territory alignment and call planning by incorporating healthcare system and payer networks that are part of the patient journey in the treatment of their disease.
- Create "bridge" roles within the pharma company that provide for linkages in the processes, methods, and data needed to solve new commercial problems. This means that the problems and solutions of tomorrow will involve interdisciplinary thinking and action.
- Develop a continuous "experimentation" mentality to create new ideas for commercial implementation. This means creating something like a Center

for Commercial Operations Excellence that is an incubator of such ideas.
- Recruit and develop new talent that can operate across traditional commercial boundaries to solve more complex issues.
- Find and partner with appropriate third-parties who have the experience to facilitate this commercial transformation across all the above dimensions for long-term success.

Crunch time

This is a critical time for the pharma industry and for executives; perhaps the most challenging of all. Companies are in the vortex of external converging forces that require change from pharma executives to move their organizations in new directions. President Trump and the changing political landscape are accelerating the need for dramatic new thinking. These shifting political trends are not the cause of such changes, but merely reactions to the current structural cost imbalances relative to the public's perceived value of the new specialty medicines coming from the industry. Whether or not President Trump runs and wins again in 2020, there are warning signs for Republicans from the 2018 midterms (14). A Democratic party victory of the White House in 2020 will not change forces already set in motion. A large Democratic party victory in the 2020 presidential election, with coattail effects expanding their majority in the House, and possibly resulting in a majority in the Senate, will only quicken the pace of political pressure on the industry. The pharma industry may find themselves in an even worse situation than they face today...

The industry reaction to the high cost of prescription drugs has been positive – for example, the new PhRMA-member TV DTC guidelines that should improve transparency by providing patients with cost and financial assistance information are helpful (15). This was also a reaction to a policy item in President Trump's American Patients First blueprint. But this approach will only serve as a band-aid: more fundamental changes are needed. The long-held "volume-based" CMD by the industry has been, in our opinion, a major driver of the adverse situations now facing pharma companies. The need is a "value-based" CMD that focuses pharma companies more on driving health and economic outcomes. The time to act is now while companies still can mold and select the path they wish to choose. Those companies who react late to changing market and environmental forces will find themselves in a long-term disadvantageous position. In closing, companies must "choose wisely," as the Grail Knight famously said to Indiana Jones, regarding his life or death choice: "But choose wisely, for while the true Grail will bring you life, the false Grail will take it from you."



George Chressanthis is Principal Scientist and Charlie Thompson is a Principal at Axtria. This article has been co-published with Axtria: https://bit.ly/2HfgKSN.

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A Knight's Tale

Sitting Down With… Sir Alasdair Breckenridge; Chairman of the Advisory Board, the Centre of Regulatory Excellence of the Government of Singapore; Advisor, Sativa Investments; member of The Pistoia Alliance Advisory Board.

Did you always see yourself becoming a scientist?

My ambition in years gone by was actually to become an economist – my father was a banker after all. But, ultimately, pharmacology chose me.

After completing my medical degree at St. Andrew's in the UK, I took on a position at the Royal Postgraduate Medical School (RPMS) where I was offered a position in the new pharmacology department. The department's approach to pharmacology meant that clinical pharmacology (which focused on the medical aspects of the field) and basic pharmacology (which looked towards physiology as its science) existed in two separate spheres. I was compelled to take the position because I felt it was imperative that these two branches of the same field be more closely tied together. It has always been my feeling that if these two areas are able to progress together, both industry and academia would be able to see greater advances.

What moments in your career stand out?

In 1974, as the Head of Pharmacology and Therapeutics at the University of Liverpool, I was able to take the reins and develop a department focused on combining basic and clinical pharmacology – a first for the UK. Though I have been knighted and received various accolades throughout my career for my services to medicine, the work of my colleagues and I changed the way an entire area of science was approached. And that is undoubtedly the highlight of my career – and a feat I am wholeheartedly proud of.

How did regulation become such an integral part of your career?

I've always had an interest in drug safety and the issues pertaining to it. My training at the RPMS was largely based on the subject, and there were safety concerns about some anti-hypertensive drugs and diuretics at the time. My work involved investigating these issues through the lens of clinical pharmacology and, as part of a natural progression, the draw of drug safety led to a career in regulation.

In 1982, I accepted my first position in pharmaceutical regulation when I was appointed to the safety sub-committee of the Committee on Safety of Medicines, UK, and was made chair of the organization in 1999. When the Medicines and Healthcare products Regulatory Agency (MHRA) was formed in 2003, I was invited to chair the organization – and did so for 10 years.

Though the MHRA is now an unshakable institution in drug regulation, there was a great deal of headbutting when the MHRA was first formed. The agency was an amalgamation of the well-established Medicines Control Agency (MCA) and the Medical Devices Agency (MDA), which was the smaller of the two agencies and run by engineers. Coming from different disciplines, the agencies had different focuses, and many difficult conversations were needed to allow the MHRA to run smoothly; thankfully, both sides were able to discover a common language.

Is regulation still a passion?

Much of my career has been defined by regulatory affairs, and though I'm no longer with the MHRA, I certainly haven't left the field behind! In recent years, I've had the opportunity to explore the international regulatory sphere. I have been a partner in the US life sciences management consulting and contract development organization, NDA Partners, since 2013, and I also worked in Singapore at the Centre of Regulatory Excellence (CoRE) for several years. The South East Asian market is growing and it is essential that the quality, safety and efficacy of drugs used in the region be assured. CoRE was developed as part of a tripartite arrangement funded by the Singaporean government, the National University of Singapore and Duke University, and is the first center in South East Asia dedicated to regulatory affairs. The lack of uniformity in regulatory standards across the region means that, when a drug is approved for use in one country, it hasn't necessarily met the regulatory standards of neighboring countries. Our aim is to streamline the regulatory process, improving the accessibility to drugs across the region.

How will Brexit affect the pharma industry?

The collective consciousness of the UK is focused on Brexit and not without good reason. For those of us in the UK, it will affect almost every aspect of our lives moving forward, and with each passing day, the uncertainty about our future grows. Though the state of our fishing industry and bottlenecks at ports are conversation points for every concerned member of the public, the future of the pharma and healthcare industries are often neglected in public discussions about our departure from the EU. The ramifications of leaving the EU are still very much unclear. But a hard Brexit would spell disaster for the pharma industry and from a regulatory standpoint, the UK will have to tread a very careful path to prevent us becoming isolated. And without the structure of the EU's regulatory system, it is more than likely that the UK will be left in the dust, forced to pay higher tariffs and exposed to delays in the introduction of new products to our market.

Even though Brexit has the potential to mark the start of dark period in the history of UK pharma and science, it could present the opportunity for positive change. The UK will have to build strong partnerships and increase collaboration with foreign regulatory bodies like the FDA and the Therapeutic Goods Administration in Australia to keep its head above water – this is something The Pistoia Alliance and I are helping the industry to understand.

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