

the Medicine Maker™

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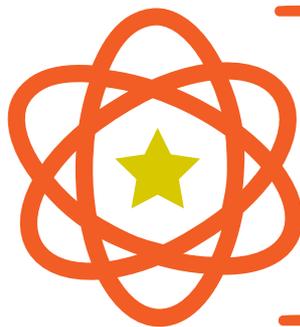
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Cleston Oxendine
Senior Research Associate
QC

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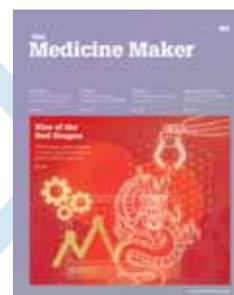
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Drug substance

Drug product

Online this Month



Looking Back

As the year comes to a close, we look back on some of the most popular cover features published in The Medicine Maker. If there are provocative topics you'd like us to publish in 2019, then get in touch with our Editor, stephanie.sutton@texerepublishing.com.

May

I'm a (Biosimilars) Believer!

What successes has the biosimilars field seen? What hurdles remain? And why does the true potential of biosimilars remain untapped? We invited four gurus to discuss the issues.

<https://bit.ly/2Ik2iO>

July

Make China Great Again

China wants to occupy the highest parts of global production chains. Find out what non-Chinese pharma companies need to know about the "Made in China 2025" initiative.

<https://bit.ly/2Pvo4bG>



August

Standing Up for the Invisible Manufacturers

Learn the story behind the Pharma & Biopharma Outsourcing Association – and why, historically, contract manufacturers have been overlooked by regulators and legislators.

<https://bit.ly/2wEbTTn>

October

Time for Pharma to Deliver?

Every day, pregnant women must make decisions and balance the risks to their own and unborn children's health when deciding to take – or not to take – medications for which no clear guidance is available.

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Celebrating a year of innovation in drug development and manufacturing technologies.

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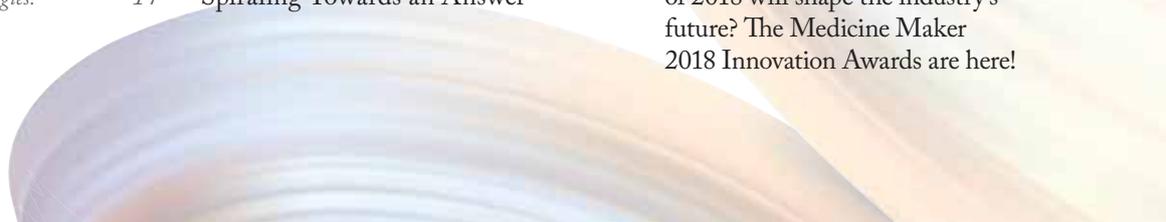
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Which top drug development and manufacturing technologies of 2018 will shape the industry's future? The Medicine Maker 2018 Innovation Awards are here!



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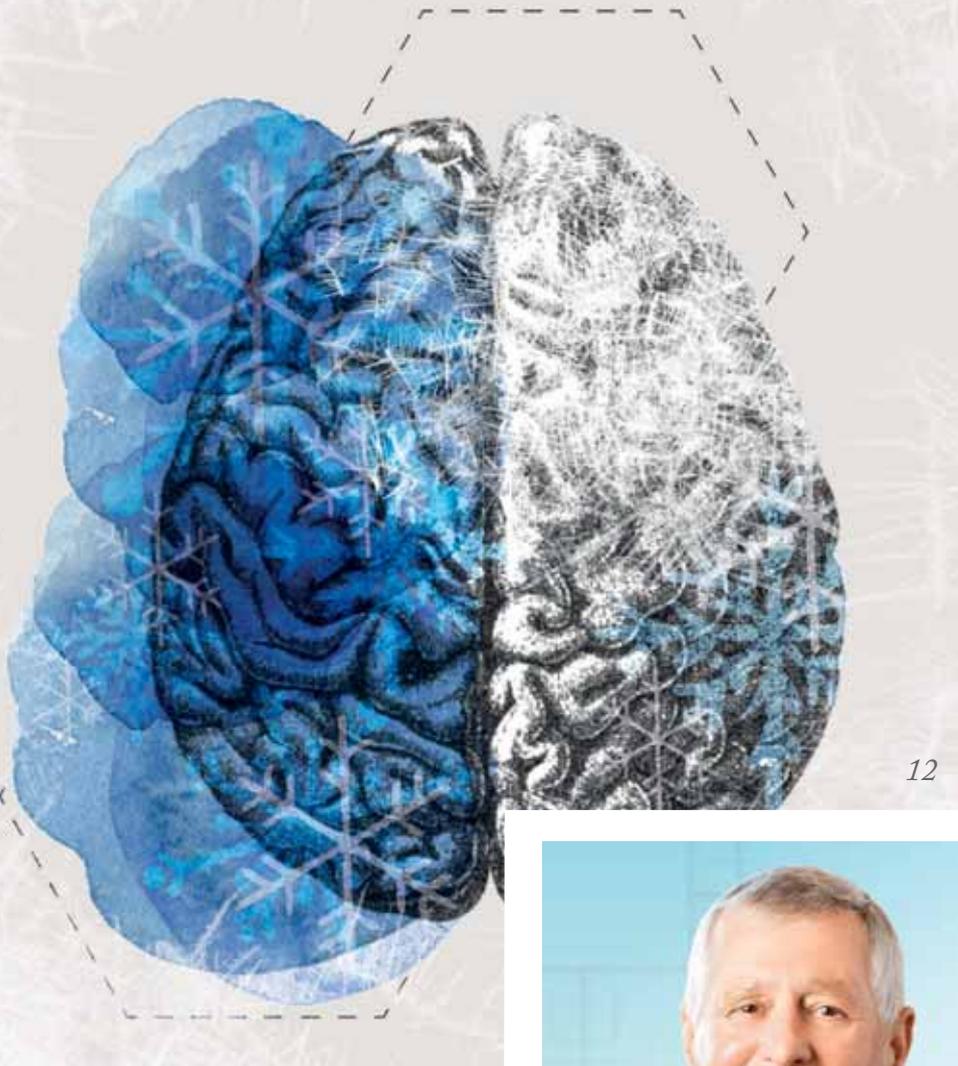
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2018 - 17169 10/2018



Welcome to our final issue of 2018 – a year that will likely be best remembered for the controversy surrounding the birth of the first gene-edited babies – twin sisters, Lulu and Nana – in China.

But Jiankui He – the scientist responsible for the “experiment” – will never be mentioned in the same breath as Edward Jenner, Alexander Fleming, or any other pioneering biomedical scientist of the past or present. If the claims made in He’s presentation to the International Human Genome Summit in Hong Kong are true, then his work falls far short of justifying the enormous risk involved – worse still, the radical research may have failed to achieve its basic aim.

He set out to create an HIV-resistant baby by using CRISPR to edit CCR5 – a gene encoding a receptor that plays a major role in the infection process. He told delegates that he chose CCR5 because some people naturally carry a mutation in CCR5 – a deletion known as delta-32 – which inactivates the gene. But according to several experts, the data presented suggest that both of the babies’ cells harbor multiple edited versions of the CCR5 gene – none of which are identical to the delta-32 mutation (1).

Before implanting the embryos, He had no way of knowing for sure if either of the twins would be protected from HIV – and we still don’t. Nor do we know if the new mutant genes will have any deleterious effects, as they have not even been studied in animal models. Despite all the red flags and ethical issues, the Associate Professor from the Southern University of Science and Technology in Shenzhen went ahead with the pregnancy anyway in the hopes of protecting the twins against a treatable disease.

One day (perhaps far in the future), we may be able to eradicate life-threatening diseases using embryonic gene editing, without the risk of off-target effects. And even then the question of whether we should do so is by no means straightforward. But in the present day? As discussed on page 10, He’s work looks destined to set the field backwards, and who knows how far?

What a stark contrast to the amazing work emanating from the cell and gene therapy field as a whole. John Rasko, President of the International Society for Cell and Gene Therapy (ISCT) and one of the authors of our supplement that accompanies this issue, says he will tell his grandchildren how 2017 was the year when the field hit the mainstream. Clearly, it hasn’t been plain sailing (and we present more than a few challenges in our supplement), but with perseverance, good science, and a clear unmet need in mind, it’s entirely possible to achieve great things under the full scrutiny of ethical and regulatory approval. Let’s hope the year 2019 follows the latter example.

Reference

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James Strachan
Deputy Editor



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

Withdrawal Symptoms

As UK politicians debate the merits of the Prime Minister's Withdrawal Agreement, we debate its potential impact for pharma...

The UK parliament is set to vote on the draft withdrawal agreement from the EU – concluded after many months of negotiations. EU leaders have already approved the “deal” but, at the time of writing, it remains to be seen as to whether UK members of parliament will follow suit. If the agreement passes, the UK would enter into a 21-month transition period – which may be extended by mutual consent – allowing time for further negotiation of the future agreement. Until December 2021, EU law would still apply in the UK, but Britain would not have voting or representation rights on EU bodies.

With over 500 pages of legal text to consider, we asked three experts whether, in their opinion, the Withdrawal Agreement should allay the fears of pharma companies.

David Jefferys, Senior Vice President for Global Regulatory, Healthcare Policy and Corporate Affairs for Eisai Europe, and Chairman of Eisai's Global Regulatory Council

We as a company, and I think all the pharmaceutical industry, welcomes the agreement between the UK and the EU 27 because, if ratified, it will provide the 21-month transition period and avoid the UK leaving the EU with no agreement in place. The industry has worked tirelessly to address the requirements of such a “hard Brexit” – and expended considerable

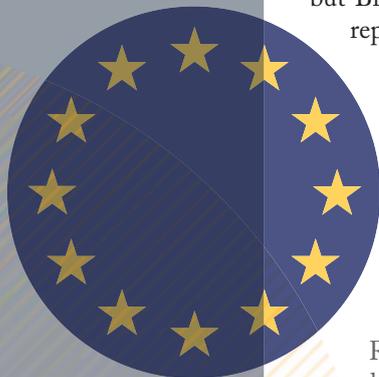
money and resources. Even so, there are issues outside the control of the industry that could disrupt global supply in the pharma sector. We need the extra 21 months to ensure the optimal supply of medicines to patients across Europe, and for there to be negotiations on an agreement which benefits all stakeholders, especially patients.

Our long-term aspirations are clear in that we wish to see close collaboration and co-operation with the EU 27 regulatory system for pharmaceuticals and frictionless trade. The very recent changes in the Political Declaration are helpful in that clause 24 now states that parties will explore the possibility of the UK co-operating with union agencies such as the EMA. We also welcome the statements concerning ongoing participation in union programs in science and innovation and the reference to cooperation on “emerging threats to health security in a consistent manner.” If the deal is ratified as we hope, then the focus switches to the extensive negotiations on the final withdrawal text for December 2020.

Richard North, former research director in the European Parliament and Environmental Health Officer, author, and blogger at eureferendum.com

The deal, if it is agreed and ratified, gives a transition period that may be extended for up to two years. Thus, as long as the deal is not turned down – which is, as yet, not certain – during the period, free movement of goods is more or less assured. This will at least give time for industry to lobby hard for a workable long-term solution and allows adjustments to be made to accommodate changing conditions.

The worst case scenario, of course, is that the deal is rejected. But even here, the industry has some leverage in that the EU 27 will not be able to access products holding UK market authorization. That undesirable situation may pave the way for a post-Brexit “mini-deal,” which will



restore some functionality to the market.

However, as long as the immediate downside of the Brexit process is uncertainty, it cannot yet be said that recent events have resolved anything. We still wait to see where our future lies, in a very volatile and uncertain trading environment. It may not be until well into the New Year that we can confidently see our way forward, and then only for a limited period.

Alex Stojanovic, researcher at the Institute for Government, an independent think tank based in the UK

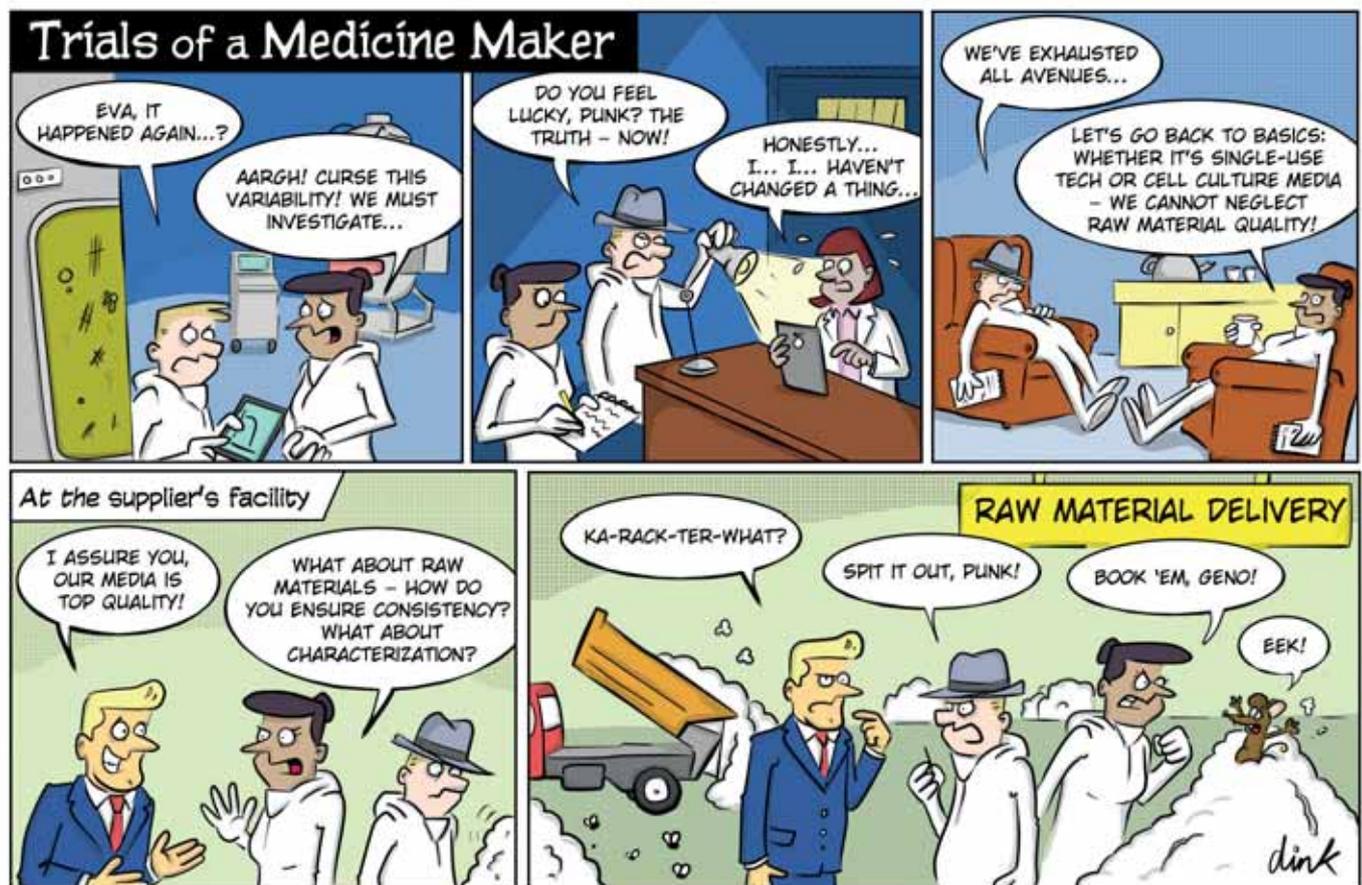
For pharmaceutical companies, the Prime Minister's deal is no panacea. If it ever came into force, British-based marketing authorizations would no longer be valid in the EU. There is nothing on participation in the EMA, and unless you're based in Northern Ireland, it leaves in place a document check and possible regulatory controls at the border that could interrupt port logistics.

For all that, there are some real positives. The deal's establishment of a customs territory would at least remove the requirement to prove the origin of goods. For complex products like medicines with many stages of synthesis, this removes one

source of substantial cost. It also comes with a political declaration that, while not legally binding, does provide for the possibility of a softer Brexit than the EU had originally outlined in their mandate for the future relationship. Specifically, it does acknowledge a link between aligning to EU rules and the incidence of controls, even if this does not quite concede to the possibility of "frictionless trade."

But the biggest plus for pharmaceutical companies is time. The transition and option to extend means companies have a lot more breathing space to make the necessary preparations.

For more adventures featuring Gene and Eva check out our website: themedicinemaker.com/additional-data/cartoons
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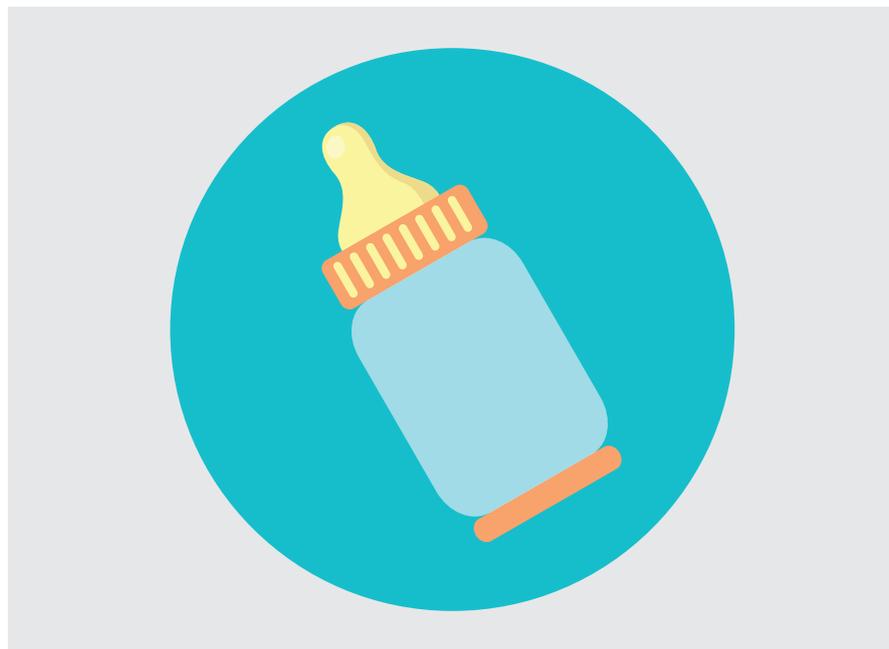


Crossing the Rubicon

What does the controversial genome editing work of Jiankui He mean for biomedical research?

A scientist has received international condemnation in the genetics field after claiming to have produced the world's first gene-edited babies using CRISPR technology. In videos posted by his lab to justify the work, Jiankui He, an Associate Professor at the Southern University of Science and Technology in Shenzhen, China, says the gene-edited twin girls were born as “healthy as any other babies” (1). The gene editing was conducted after IVF, when each embryo was just a single cell, to modify the CCR5 gene to block HIV infection. The girls' father was HIV positive and He says that the twins will be monitored over the course of the next 18 years.

“I understand my work will be controversial, but I believe families need this technology and I'm willing to take the criticism for them,” He said in one of the videos. He says he targeted HIV because of “safety”, adding that CCR5 is one of the best studied genes and many people have natural genetic variation that disables the gene to prevent HIV infection. He claims it was the “simplest gene surgery possible.” Gene editing to correct broken genes to perhaps target familial cancers or muscular dystrophy would be more complex.



CRISPR's ability to edit genes, coupled with its cost-efficient production and high degree of fidelity, make it an attractive method of genome editing, but navigating the ethical minefield associated with its use seems to be challenging for the research community. The risk of harm to human life and its potential to cause environmental damage limit its applications. Current iterations of the technology make it possible to introduce off-target mutations (which introduce mosaicism and off-target mutations (which can be deleterious) into human DNA. Forty countries including the UK, US and China have banned or discouraged the use of genome editing.

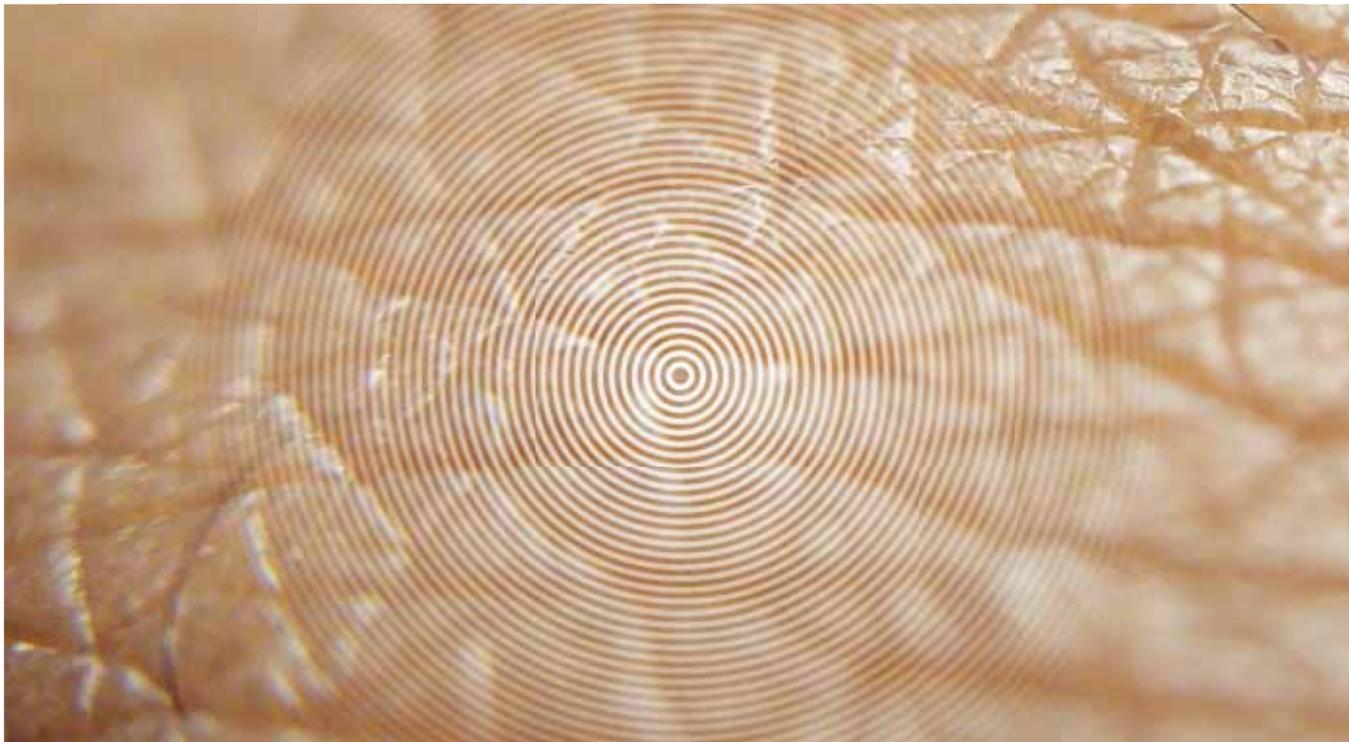
Gaetan Burgio, Geneticist and Group Leader at Australian National University, who tweeted about a panel discussion that He was involved in at the Human Genome Editing Summit where he discussed the work, said that the method He outlined doesn't do enough to rule out mosaicism or deletions (2). The scientific community has called for an independent peer-review of the trial to assess the validity of the claims made by He.

The global scientific community fears He's work could hinder the future of CRISPR by exacerbating the public's scepticism and forcing the hand of regulators, compelling them to put even stricter rulings into place about the use of the technology.

The Southern University of Science and Technology says it was not aware of the project and that He had been on paid leave since February. A variety of mixed reports are now circling in the media regarding He's location. Some have reported he is under house arrest in China, but the Southern University of Science and Technology says that this information is not accurate. China's Vice Minister for Science and Technology has called for a suspension of any scientific activities by those involved in He's work.

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Skin Deep Problems

A flexible, synthetic patch helps eliminate the toxicity and invasiveness associated with long-term drug delivery

In most cases, conventional drug delivery works very well, but what about when first-pass metabolism interferes with the drug to render it useless? Or when patients simply refuse to swallow tablets? Injectables are also not immune to problems, given that a number of patients may be needle-phobic.

For many years, there has been intense discussion in the industry about the benefits of transdermal delivery. One common approach to dermal drug delivery is the use of silicon nanoneedle patches, but while these do show potential, they

can only be used on a short-term basis. Commercially available patches are often rigid and may cause damage to the tissues around the site of injection. Chi Hwan Lee, Assistant Professor of Biomedical Engineering at Purdue University, along with his colleagues, has developed a flexible, transparent patch capable of delivering drugs to a target site without causing discomfort to the patient. The nanoneedles on the patch reduce the invasiveness and toxicity associated with long-term drug delivery (1).

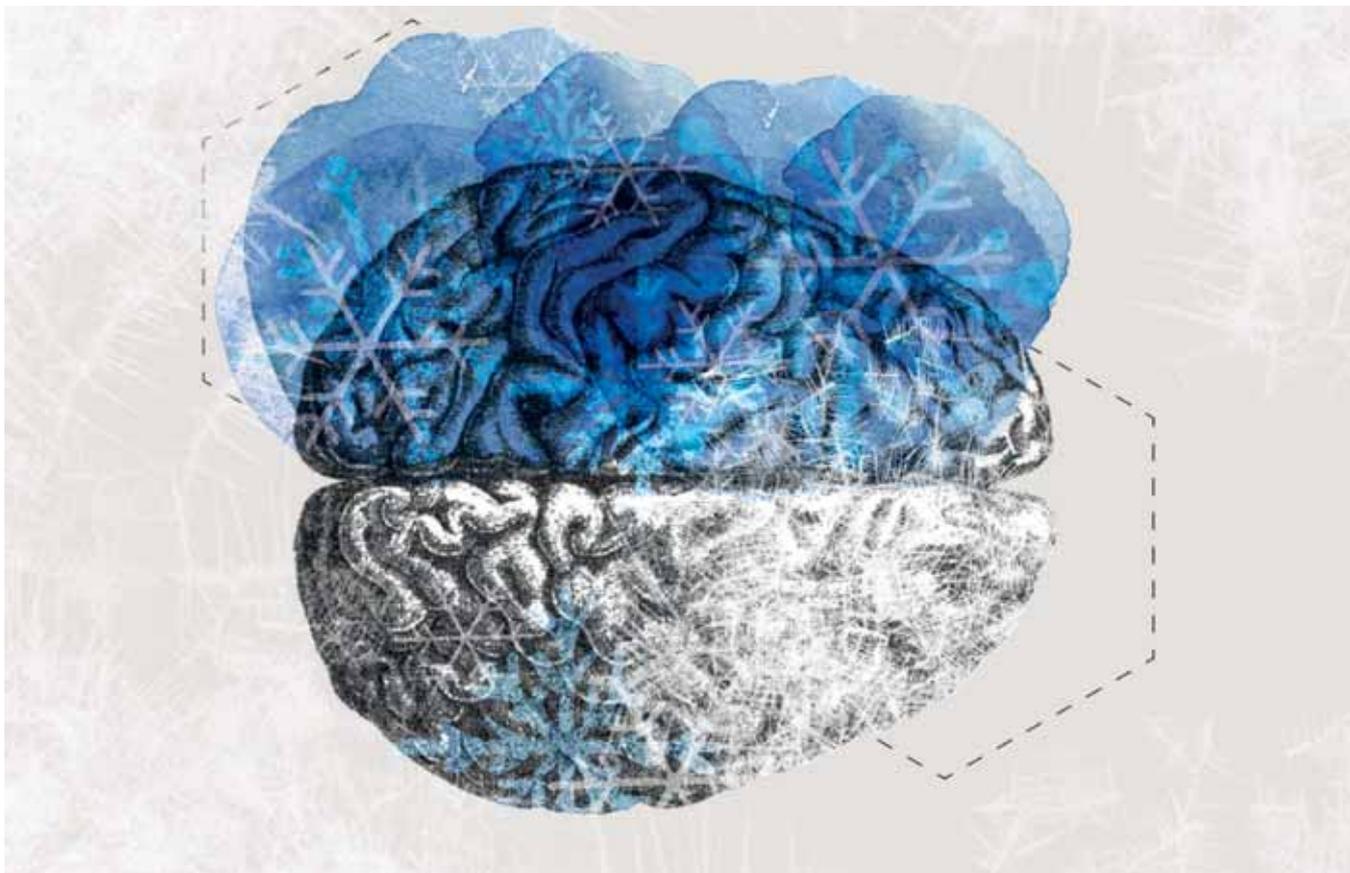
“Our design really focused on making transdermal patches practical for use over extended periods. The flexibility of the silicon nanoneedles allows for injection on curved surfaces, such as the fingers, neck or elbow. In fact, several of them can be injected into a single biological cell at the nano-resolution scale in a minimally invasive manner,” Lee explains. “Another feature that sets the patch apart from traditional nanoneedle patches is its

transparency. This means that real-time interactions between cells and nanoneedles can be observed. Previously, patches were opaque, limiting our ability to monitor the extent of cellular damage that was occurring.”

The team is testing the operational validity of the patch for treating cancerous tissues and monitoring electrical activity in cells. They are also looking at tweaking the system in other ways. “We recognize that while our patch minimizes tissue damage in comparison to previous technologies, it doesn’t completely mitigate the problem. We hope to reduce the size of the needle tips on our patches to help avoid any unnecessary tissue damage,” says Lee.

Reference

1. CH Lee et al., “Flexible elastomer patch with vertical silicon nanoneedles for intracellular and intratissue nano-injection of biomolecules,” *Science Advances*, 11 (2018).



Holding Back the Years

Seeking inspiration from plants in the fight against Alzheimer's disease

A class of potential therapeutics called geroprotectors aim to tackle the onset of age-related disease, and are associated with slowing the rate of biological aging. Now, researchers at the Salk Institute for Biological Studies have identified a subset of geroprotectors – dubbed “geroneuroprotectors” – that they believe could be valuable as drug candidates for AD. They found that these compounds reduce the molecular

markers of aging and AD itself (1).

“Old age is the major risk factor for many diseases,” says Pamela Maher, Senior Staff Scientist at the Salk Institute. “The idea is that if you can slow down the aging process then you can slow down the development of these diseases.”

The group used bioactive compounds derived from plants as the basis of their research. “It’s very easy to forget that plants were the medicines of the original pharmacopeia. Many established drugs, such as aspirin, are based on plants. So, it was only rational for us to begin our research exploiting the potential of plants,” Maher says.

Fisetin (a polyphenol found in a variety of fruit and vegetable products), curcumin (derived from turmeric) and three drug candidates derived from these

two widely available compounds were assessed to determine their ability to slow down the progression of AD. The Salk researchers found that CMS121, CAD31 (fisetin derived) and J147 (curcumin derived) were able to curb the onset of dementia-like symptoms and expand the median lifespan of mice and/or flies. Though the compounds did not have an effect on maximal lifespan, the group notes that an extended median lifespan is associated with longer periods of good health and the reduced likelihood of disease development.

Reference

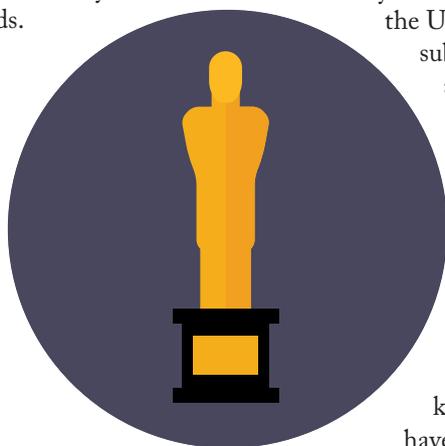
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Business-in-Brief

Oscars of science, drug shortage reporting requirements, and a new gene therapy... What's new for pharma in business?

Awards

- Shire's Los Angeles Building 8 facility has been named the overall winner of the ISPE Facility of the Year Awards. The company also won in the "Facility Integration" category. The project involved construction of a 120,000 square foot purification facility, which needed to be integrated into an 11.6-acre campus with eight other buildings and space constraints on all sides.
- The Oscars of Science Awards took place in early November, with a number of prizes being awarded in life sciences, including for Joanne Chory (Salk Institute for Biological Studies and Howard Hughes Medical Institute), Don W. Cleveland (Ludwig Institute for Cancer Research at University of California, San Diego), Kazutoshi Mori (Kyoto University), Kim Nasmyth (University of Oxford), and Peter Walter (University of California, San Francisco).
- For his impressive business acumen and leadership, Nik Kotecha OBE, Chief Executive of Morningside



Pharmaceuticals, was named the Innovation Entrepreneur of the Year at the annual Great British Entrepreneur Awards. The company specializes in the manufacture and supply of generics and was the first to launch a generic version of the contraceptive pill in the UK.

Shortages

- EpiPen shortages are affecting many countries, including the UK, which has subsequently authorized 300 µg pens to be used beyond their expiration dates, as well as lowering the weight threshold for use of the higher dose EpiPen to 25 kg. The shortages have been attributed to manufacturing issues at a Pfizer plant, which makes the pens for Mylan.
- Mandatory reporting requirements for sponsors will come into effect in Australia on January 1, 2019. Shortages of critical medicines will need to be reported to Australia's Therapeutic Goods Administration (TGA) within two working days, and non-critical shortages within 10 working days. TGA will also have greater powers to penalize sponsors who deliberately fail to comply.
- In response to ongoing drug shortages in the US,



a group of healthcare organizations has issued a series of recommendations. Released in November, the 19 recommendations made by the healthcare coalition (consisting of The American Hospital Association, American Society of Anaesthesiologists, the American Society of Clinical Oncology, American Society of Health-System Pharmacists, and the Institute for Safe Medication Practices) suggest ways in which the problem could be resolved through regulatory, legislative and marketplace changes.

Approvals

- Luxturna, a gene therapy product used for the treatment of a rare retinal dystrophies caused by RPE65 mutations, has received EMA approval. This comes almost a year after the product had been approved for use by the FDA. The therapy, produced by Novartis, can be used to treat both adults and children.
- The FDA has cleared Vitrakvi (larotrectinib) for use. The "tissue agnostic" treatment doesn't target the specific location a tumor originated from; rather it treats cancers based on common biomarkers. This is only the second time a drug of this kind has been approved by the US regulator.



Spiraling Towards an Answer

Researchers capture the interactions of antibodies with the parasite responsible for malaria for the first time

What begins as a tiny bite from a mosquito, driven by its thirst for blood, can transmit an illness that causes nearly half a million deaths every year: malaria. And though \$2.7 billion was spent in an effort to control and eliminate the number of cases of malaria worldwide, risk of transmission remains high, with case incidence steadily rising in the Americas, South-East Asia, Western Pacific and African regions (1).

The battle against malaria has been long and arduous for scientists and healthcare professionals on the front line. The sheer structural complexity of *Plasmodium falciparum* – the parasite responsible for causing the deadliest form of malaria – makes it a particularly difficult disease to treat.

RTS,S is a malaria vaccine that has demonstrated protective effects in both children and infants – it received a positive opinion from the European regulatory authorities in July and will be rolled out through a pilot introduction in areas of three African countries beginning in 2019. Scientists at the Scripps Research Institute and PATH's Malaria Vaccine Initiative

have been conducting a cryo-electron microscopy (cryo-EM) investigation, as part of an international effort to further improve the vaccine. Specifically, the researchers looked at antibodies isolated from people who received the RTS,S vaccine and revealed, for the first time, how they interact with *P. falciparum* by locking the circumsporozoite protein on the parasite surface into a spiral-like conformation (2). “We were absolutely delighted to see the first images. No-one could have predicted that we would see a structure like this,” says Ian Wilson, Professor at Scripps Research and co-corresponding author of the study.

“We even remade the sample to validate our results,” adds David Oyen, research fellow at Scripps Research and co-first author of the paper.

Capturing how the human immune system interacts with *P. falciparum* was previously considered intractable; imaging techniques simply weren't able to resolve the details.

“Since the CSP contains a multitude of low complexity repeats, different antibodies can bind at the same time, resulting in heterogeneity that is nearly impossible to study and made it crucial for cryo-EM to be used,” says Andrew Ward at Scripps Research, and a corresponding author on the paper.

The team now says it will screen a variety of antibodies from different sources to map the structural features and configurational changes that occur when they bind to circumsporozoite proteins – and hope it will reveal new information about how to block the parasite's lifecycle in humans. Collaboration with other labs to design new immunogens based on their cryo-EM images is something the team is

keen on pursuing.

“If we can learn how to focus the immune response on the key structural and functional features of the malaria antigen, we can really make a difference in trying to control this disease,” says Wilson.

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Single-pass TFF is a convenient means of reducing volumes, column sizes and hardware costs, as well as eliminating tank bottlenecks – and can be powerfully combined with single-use technology.

By Emily Peterson

In the early days of the biopharmaceutical industry, the costs of production received little attention given that profit margins on lifesaving drugs often tipped over 100 percent (1). But as the number of blockbuster drugs slowed and competition in the sector increased, the industry began to think hard about how to reduce manufacturing costs. Facilities in those days exclusively used inflexible, hard-piped equipment and stainless steel bioreactors and tanks. More recently, single-use technologies have emerged, presenting an attractive alternative that allows companies to eliminate cleaning validation requirements, while reducing the risk of cross contamination. Plus, faster turnaround between campaigns and the reduced time for new facilities to become operational are a good match for companies with several products in the pipeline – and the figures bear this out.

In 2006, 21 percent of bioreactors were single use, but by 2017, the number rose to 80 percent (2). There has also been a similarly rapid growth in the adoption of single-use mixing systems, which increased by 58 percent over the same period. The growth in the adoption of some new(er) single-use equipment, such as membrane adsorbers and perfusion/tangential flow filtration devices, has been slower (37 percent and

38 percent, respectively), but these technologies do mesh well with the industry's shift away from batch processing.

Single-pass tangential flow filtration is one such technology that I see in an increasing number of applications, including for processing monoclonal antibodies (mAbs), vaccines and plasma. Tangential flow filtration (TFF) is widely used for downstream processing applications and involves concentrating product through volume reduction, followed by buffer exchange via diafiltration to achieve high yields. Traditional TFF requires multiple passes through a system, using a pump to drive feed through a filter and sending the retentate back to a tank for another pass through the system.

Single-pass TFF, on the other hand, does not recycle the retentate because the TFF sufficiently concentrates the product after a single-pass through the filter assembly. This results in a much smaller footprint in any unit operation you want to use it with. For example, imagine bringing in a new molecule and the tank doesn't have sufficient capacity to hold the volume. You may decide to implement a volume-reduction step, and single-pass TFF is a great option here because you can reduce volume before reaching the tank capacity without adding additional stainless steel piping to your existing manufacturing line.

Single-pass TFF can also be used in process intensification; specifically, to intensify your chromatography and filtration steps. This is simply a case of doing a concentration prior to loading onto a column. This way, you can increase the dynamic binding capacity of your resin, which allows you to use less resin in your process step. This will greatly reduce the cost, column size and buffer usage – everything that goes along with larger feed volumes.

Another great application is for high-concentration formulations. Single-pass

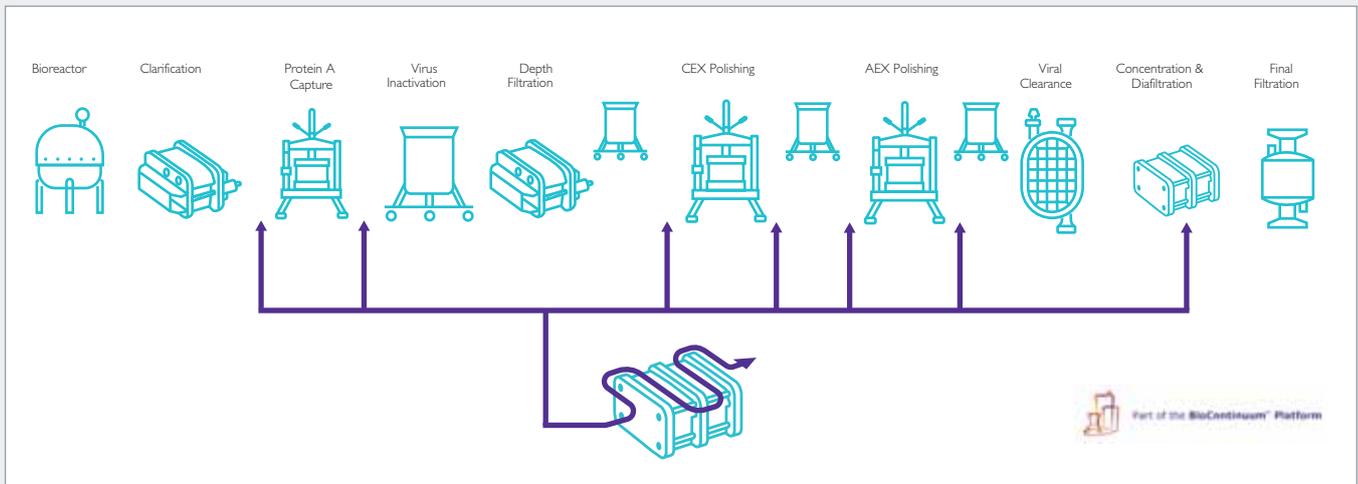


TFF typically runs at much lower cross-flow rates when compared with traditional batch TFF – in the region of one L/min/m² or lower, as opposed to the 4-6 L/min/m² you get with batch. This eliminates the need for larger pipes and pumps, resulting in significant equipment cost savings. And because there isn't as much dilution at the end of the process, it can be much easier to achieve higher concentrations when compared with batch TFF.

Finally, single-pass TFF also offers safety benefits. For example, with batch TFF you're repeatedly concentrating – passing a volume of fluid over and over again with multiple passes – which introduces the chance of damaging your molecule. Single-pass TFF is a much gentler operation, which can be a big bonus if your molecule is shear-sensitive.

Single-pass TFF and single use
Single-pass TFF can be powerfully combined with single-use technology. Traditional TFF is hardware driven – you have to install devices and holders and there's some cleaning and pre-use work that's related to traditional TFF. There are also a lot of stainless components that restrict moving and scalability for platforming. In addition, once you're done processing, you have to disassemble the units, clean them and discard them. This certainly goes against the overall industry trend towards disposable, more flexible, systems.





Single-pass TFF can be accommodated anywhere in a process where volume reduction is needed.

There are single-pass TFF options, such as Merck's Pellicon® capsule, which come holderless and pre-sterilized – reducing setup time and eliminating cleaning altogether. There are also no diverter plates, so to get started, you simply connect capsules in a series: retentate to feed, feed to retentate. Essentially, you plug it into your process and you're ready to go. At the end of your process run, you throw the capsule away so you don't have to worry about bioburden or operator safety.

Single-pass TFF is easy to get started with in that there's no need for pre-cleaning or pre-conditioning – you just have to flush the water that's been there for shipping purposes. Then, it's simply a case of finding the right conditions (although granted this can be a little tricky for someone who has never done it before). The biggest variable is figuring out the correct back pressure, which is feed specific and, therefore, depends on your starting concentration – this can sometimes involve a little experimentation to find the optimal pressure. Next, it's a case of running your feed flux excursion at the different flow rates. Usually, I start out at one L/min/m² and decrease from there. By decreasing the cross flow rate,

you increase your conversion rate, which allows you to dial in the kind of conversion you're looking for.

One great advantage of single-pass TFF is that you can collect data over multiple sections to figure out how many sections you'll need in the end. For example, if you want more time to consider, you can decrease your area and increase your time by turning down the cross flow rate. Once you have your back pressure and desired cross flow rate based on conversion or volumetric concentration, you just have to increase your area based on process volume and desired process time. Essentially, once you know your cross flow rate, scale-up volume, and time that you want to process (depending on how much area you use), you're looking for the same number of sections and the same pressure profile across the devices.

Once you've overcome these steps in process development, single-pass TFF is simple to use. And for companies looking to reduce volumes and column size – especially in existing facilities where space may be limited – as well as eliminate tank bottlenecks, it's a great option. It's also an enabling technology for companies looking to transition towards more continuous and single-use processes, where high

product quality, speed to market, resource conservation, and safety are paramount. The biopharmaceutical industry is clearly trending in this direction, and I believe we'll see newer technologies, such as tangential flow filtration systems, become more widely adopted over the next few years – as mixing systems and bioreactors have. From a personal perspective, having worked in TFF for just under four years – and the industry as a whole for almost two decades – customers seem very positive about the technology and I see a growing interest in combining single-pass TFF with single use for a number of applications.

Emily Peterson is Senior Development Engineer at Merck.

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

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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

Medicines Anywhere, Anytime

Why use a huge manufacturing facility when biological medicines can be made in a suitcase?



By Govind Rao, Center for Advanced Sensor Technology, University of Maryland, Baltimore, USA.

Biologics, are currently manufactured at centralized facilities according to rigorous protocols, but such facilities require multiple years to design, build, and qualify and are just not suited to respond to rapid changes in demand. Furthermore, should a manufacturing facility go offline, perhaps because of a natural disaster, it is likely to result in severe shortages that would adversely impact public health – this happened in 2017 after Hurricane Maria hit Puerto Rico.

Another huge issue in the industry today that should not be ignored is the fact that pharma suffers from enormous expenditures that, nonetheless, results in relatively few new drugs and therapies reaching the market. Novel enabling approaches, which eliminate practical development limitations and ultimately lower production costs,

will be indispensable in meeting these challenges.

The Defense Advanced Research Projects Agency (DARPA) created a program to fund the development of Biologically-derived Medicines on Demand, called the Bio-MOD program – and I was fortunate to receive funding under this program. The program is primarily driven by a need for medicines in the battlefield and austere locations, but it also considers the factors mentioned above. The requirements of the program were to develop a technology that could manufacture biologics at the point-of-care in under 24 hours under GMP-like conditions.

It was a daunting challenge and my team and I quickly realized that we could not achieve this with conventional cell-culture based approaches – growing the cells alone would take longer than the specified period. Fortunately for us, the availability of cell-free expression technologies (also called in vitro translation or IVT) had evolved

“It was a daunting challenge and my team and I quickly realized that we could not achieve this with conventional cell-culture based approaches.”

“In my view, this is a new vision that can potentially create therapeutics not only for the point-of-care needs of prevalent diseases, but also for orphan diseases and rare conditions.”

to the point where they could meet our needs. The Bio-MOD technology recently described by us combines IVT from cell lysates with microfluidic purification methods (1). The system used lyophilized Chinese Hamster Ovary (CHO) extracts, which meant that cold chain could be eliminated and allowed the system to be operated

anywhere in the world, including on a remote battlefield. Highly purified protein products are produced in a few hours using an automated platform with built-in diagnostics to monitor process consistency. This manufacturing technology essentially reduces a large GMP facility to the size of a suitcase.

However, during the course of this work, I wondered if we could make it even simpler and cheaper to use. The use of cell-free systems meant that a large number of expression platforms was available, and perhaps human blood could be a viable source as well. We conducted a study in this area – and found that we were correct (2). While the initial yields are impractically low, further development will no doubt address this current limitation. Human blood may potentially involve fewer regulatory hurdles for use in humans, and could also allow for individuals to serve as their own source for the reagents to make their own medicine – and perhaps empower people who otherwise cannot readily access or afford biologics. We have been regularly meeting with regulators to ensure that we do not get too far ahead of ourselves, and the FDA Emerging Technology Team has been very helpful in providing us with guidance.

In my view, this is a new vision that

can potentially create therapeutics not only for the point-of-care needs of prevalent diseases, but also for orphan diseases and rare conditions, which are often overlooked due to the smaller affected populations and the reduced profit margins. Bio-MOD technology combined with the use of human blood could also facilitate the fight against endemic diseases at remote and low-infrastructure areas by supplying the necessary therapeutics without the need for comprehensive and expensive development processes. In addition, colleagues working on long-duration space flight and manned missions to the Moon/Mars have also expressed an interest in the technology, as it solves the problem of biologics availability when transit times for delivery of supplies could be several months...

Finally, perhaps the ancient medical (and now largely discredited) practice of bloodletting might be re-purposed!

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Domesticating Cannabis

There is much we know about the cannabis plant, but its potential in medicine and drug discovery is largely untapped.

By Giovanni Appendino, Scientific Advisor at Indena, Italy.



Cannabis was one of the first plants cultivated by humans and it has been adapted to a variety of human needs: technical (fiber hemp), nutritional (hemp food), medicinal, and recreational (“marijuana”). But although cannabis has been “tamed”, it is far from being fully domesticated – there are too many gaps in our knowledge.

Cannabis produces a galaxy of over 150 unique isoprenylated alkylresorcinols, known as phytocannabinoids and a

host of equally unique polyphenolics (1), but biomedical interest has so far focused only on two compounds: Δ^9 tetrahydrocannabinol (Δ^9 -THC) and cannabidiol (CBD). Δ^9 -THC, a narcotic and socially divisive compound, has fostered the discovery of the endocannabinoid system, its two receptors (CB_1 and CB_2), and its endogenous modulators (endocannabinoids) – just like nicotine and muscarine did for the cholinergic system, ephedrine for the adrenergic system, and morphine for the opioid system. Conversely, CBD (e.g., Epidiolex GW Pharmaceuticals, UK) is still challenging molecular pharmacologists to unravel the molecular bases of its clinical activity in medical conditions where conventional treatment is of avail, such as genetic forms of epilepsy.

Δ^9 -THC and CBD are the easiest compounds to purify from cannabis, but some say they are only the tip of the iceberg. There is growing evidence that the cannabinoid structural motif is a privileged platform for bioactivity and that its chemical space

“Although cannabis has been ‘tamed’, it is far from being fully domesticated – there are too many gaps in our knowledge.”

is still substantially unexplored. For cannabinoids, narcotic properties are not a sequitur; just because a compound is a cannabinoid and comes from cannabis does not mean that it will be psychoactive. A small change, like shortening the *n*-pentyl residue to a *n*-propyl as in Δ^9 -THCV – the naturally occurring lower homologue of Δ^9 -THC – switches the activity from CB_1 agonism to antagonism (1), while the carboxylated native form of Δ^9 -THC (pre-THC or THCA-A) is a powerful PPAR γ agonist with remarkable neuroprotective activity and negligible activity on CB_1 (2).

While the biomedical potency of Δ^9 -THC and CBD is remarkable, there is surprisingly scarce awareness that these compounds do not belong to the native branch of the phytocannabinoid lineage. They are produced, just like all the other analogues in the plant, as carboxylated precursors, and, to a limited extent, as terpenyl esters of the carboxylated precursors. The native carboxylated forms (pre-cannabinoids or acidic cannabinoids) are thermally unstable, and are converted to neutral phytocannabinoids by loss of carbon dioxide. In turn, phytocannabinoids can be oxidized to cannabinoquinoids, another class of interesting compounds, whose instability has spurred the generation of stable semi-synthetic analogues, exemplified by VCE-004.8. This aminoquinoid is interesting for autoimmune diseases like multiple sclerosis, and has received orphan drug status by FDA and EMA for the treatment of scleroderma (in development by Emerald Health Pharmaceuticals, USA).

The chemical diversity of cannabis is, thus, not only expressed by native compounds, since acidic phytocannabinoids are generated with an expiry date and are primed to undergo a series of degradative modifications that

“All these changes are associated with distinct biological profiles – a ‘cannabinome’ that still waits to be disentangled and domesticated to the benefit of medicine.”

generate neutral phytocannabinoids and cannabinoquinoids. These are, in turn, excellent templates for the development of novel semi-synthetic analogues with superior activities. All these changes are associated with distinct biological profiles – a “cannabinome” that still waits to be disentangled and domesticated to the benefit of medicine. Cannabis has long been considered a social issue or a book to be read in Smithsonian terms – a catalogue of structures. Seeing it as a source of solutions for unmet medical needs is a big step forward, and should spark optimism (rather than skepticism) in the medicinal chemistry community.

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Are You Thinking of Scaling Up Your Stem Cell Cultivation?

Today's bioprocess professionals need to stay on top of many things: Scale-up parameters and equipment capabilities, control strategies and automation, validation requirements and documentation to name a few. New fields of applications like stem cell technology are evolving into powerful tools of the future.

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Staying Flexible

The biopharma industry offers big rewards – but it poses big risks, too. Rather than fearing the unknown, the concept of optionality can help you better manage it.

By Firman Ghouze and Uriel Kusiatin

There are few industries that illustrate the notion of “high risk, high return” better than biopharma. In terms of the huge uncertainty in predicting who will succeed and who won’t, it’s probably comparable to the music industry – it’s a very risky business.

But what if you were able to quantify and, therefore, better manage this uncertainty? This may seem like a big ask, but a tool does exist to help businesses make better decisions in a highly uncertain environment: optionality. Essentially, optionality is the concept of keeping one’s options open so that you have multiple pathways you can take instead of committing to just one – retaining flexibility versus an “all or nothing” proposition.

But despite the high uncertainty biopharma faces, it is surprising how many people involved in the field, and especially in manufacturing, have little or no real understanding of how to best assess investments in the space, and how to apply optional approaches to help them do that.



Blockbuster or big flop?

Think of the traditional process of developing a new product. If you are sitting on a new idea and you need to invest to make it a reality, you have no idea yet if your drug is going to be the next big blockbuster or a “white elephant”. Over time, as you develop the drug, the risk of failure lessens. Following this classical path, you have phase I trials that give you safety data, then phase II for post-escalation safety data, and finally phase III, which will tell you how effective the drug is. These are clear milestones to reach as you de-risk your investment and gain a clearer understanding of whether you’re going to be successful.

This is where optionality comes in – as you’re going through this process, you need to consider the manufacturing dilemmas – how to secure the appropriate manufacturing capacity for a drug that is still in development and may fail clinical trials (option to abandon)? Do you build, buy or partner (outsource to CMO)? How much capacity do you secure given uncertain demand? What flexibility in the design or contracts do you need to consider if demand is higher than anticipated (or you expand internationally sooner than originally anticipated) or is slower to ramp up (option to expand or option to contract)?

Not considering the full spectrum of options can lead to negative consequences. Take Tesla – they have a

very popular car but they can’t produce the numbers they want at the quantity and quality needed because their manufacturing strategy doesn’t align with the huge demand they are facing.

Conversely, there used to be a leader in the cell therapeutics field called Dendreon, which made some of the first cell therapies and garnered a lot of interest from the investor community.

The company had a lot of funding, and built a relatively large manufacturing hub to begin manufacture of what they anticipated would be a blockbuster. But although it did get past phases I–III, the efficacy data and reimbursement weren’t where they thought they would be, and subsequently the company went bankrupt and was sold.

So on one hand, you want your manufacturing capabilities up and running



“When it comes to introducing an optionality approach, you need an internal champion – someone who is really enthusiastic about the idea.”



to meet high demand. On the other, you don't want to invest too much too early. Optionality is how you can find the "sweet spot" to be prepared exactly when (and if) you need to be.

Embracing uncertainty

When it comes to introducing an optionality approach, you need an internal champion – someone who is really enthusiastic about the idea and will help guide their colleagues and company towards it. The key is to become more comfortable with uncertainty. People always talk about risk, because that's what they're afraid of – but risk is just one part of the uncertainty equation – the downside. There's an upside too; when you are facing risk, you are also facing opportunity. The best and worst case scenarios must both be considered, so it's not all doom and gloom!

When companies have this explained to them, they tend to be very receptive. A large part of the approach, especially in larger organizations, is bringing different departments together – marketing, new product development, R&D, clinical manufacturing and more – and taking them through this thought process, finding out what flexibilities they have, what their lead times are, and what the

budget for certain things is. You need to get people talking and thinking about these issues, as well as about the different scenarios that could happen – almost like a strategic planning exercise with uncertainty as your underlying theme.

Next, you can look at how you can use optionality for the specific scenario you're facing. For example, you're going into a new market and you decide to spend \$100,000 on market research to better understand price variability, which will take six months – this is your first investment. Then you consider your next move: should you pull back, invest in a pilot, or accelerate the investment and go for full market penetration? You need to lay out the options you have along the way and try to better understand what the key decision points along your path are, and what opportunities you have to either halt your investment or accelerate it depending on the knowledge and feedback you are gaining.

You can do this using a combination of financial options analysis combined with decision analytics to quantify your options – this is where things get technical, but it can all be done in a spreadsheet. Quantifying uncertainty can be done using, amongst other tools, Monte Carlo simulation. You can then apply Real Options Analysis to value the flexibility that decision makers have to course correct their investment decisions as uncertainty resolves itself over time. In other words, at key decision milestones, managers should stop and ask, "Okay, what have I found out? Has some of the uncertainty that I had on day zero resolved itself,

and if so can I rerun my model and come up with more precise predictions about the future now?"

Keeping options open

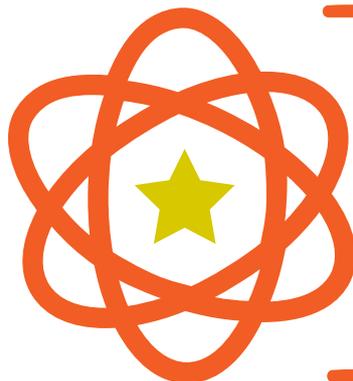
Once you have these processes in place, you can take the optional approach and apply it to almost anything – manufacturing, entering uncertain or emerging markets, choosing vendors, considering partnerships, R&D portfolio management... the list goes on. You can even use it in business development and deal negotiation to quantify the risks and opportunities of different decisions to choose the best deal. The sky is the limit!

Ultimately, optionality isn't about spreadsheets and software – it's a way of thinking about problems. It's not the way managers and leaders are traditionally taught to think, which is unfortunate because it's a valuable concept for biopharma to embrace. Everyone is familiar with uncertainty, but many people choose to ignore the things they consider unquantifiable and uncontrollable. But the tools are out there – and if you use them correctly, you can approach risk and reward in a much more structured way to make the very best decisions for your business. There is no way to eliminate risk from pharma, but one thing is certain: you can account for it.

Firman Ghouze is the Director of Commercial Strategy at GE Healthcare Life Sciences. He is responsible for developing the GE's commercial strategy and partnerships in the bioprocess space. He has worked in the biomanufacturing industry, encompassing both protein and cell therapeutics, for the last ten years.

Uriel Kusiatin is CFO of Provista Diagnostics Inc. He previously worked as a consultant developing and applying methodologies for assessing investment decisions in the life sciences using financial analysis and strategic decision-making techniques.





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Strokes *of Genius*

The 2018 Innovation Awards are here! From colorful capsules, to blockchain software, to high-tech mass spectrometers; we celebrate advances of all stripes and colors.



COC INDIVIDUALIZED CONTAINERS

Customized containers that can be designed according to patient needs

Produced by SCHOTT AG, Pharmaceutical Systems

An increasing number of drugs are administered in combination with a device to make the drug delivery process as simple and comfortable for the patient as possible. Yet challenges remain: namely, meeting the differing usage requirements of a diverse patient population. To meet this need, SCHOTT has used its expertise in cyclic olefin copolymer (COC) material to allow its customers to co-create a COC container for a device. The material's high design flexibility allows customized containers; for example, manufacturers of wearables can reduce the size or adapt the form. Each phase of the four-stage sampling process provides containers for different purposes in the drug development stage, improving the time-to-market while reducing financial and project risks.

Potential impact:

In most cases, drug delivery devices have needed to be built around the pharmaceutical packaging containers currently on the market, which means restrictions in terms of device design. By jointly developing a container made out of COC with the customer, the needs of the drug product, filling process and drug administration are met without compromising on device design. Subsequently, device manufacturers can develop more patient-centered devices for the desired patient population.

COLORISTA

Capsules with a broad selection of colorants suitable for use in major markets

Produced by Capsugel, now a Lonza Company

Colorista is a new capsule based on an “all colorants” formulation, which means that the capsules contain a selection of various colorants that offer a great deal of final choice in terms of shade and regulatory acceptability (different regulatory agencies worldwide have different requirements around color). More than 150 colors can be extracted in gelatin and 50 colors in HPMC, and the capsules are robust and resistant to fading.

Potential impact:

The color composition choice for a commercial drug product is often made after initial stability studies – and if new colors are introduced, it may necessitate additional studies, which can result in delays. Colorista allows scientists to progress with compatibility and stability testing before deciding on a color for the commercial drug product. The company hopes that the capsules will help shorten development times.



CYTO-MINE

A single-cell system for rapid biopharmaceutical discovery

Produced by Sphere Fluidics Limited

Cyto-Mine automatically performs high-throughput biopharma discovery, cell line development and monoclonality assurance. The system uses single-cell encapsulation in picodroplets to trap cells and secreted proteins. Unlike existing platforms such as clone pickers (that normally test 10,000 cells per run), Cyto-Mine offers very high throughput (up to 10 million heterogeneous mammalian cells in less than half a day) and is gentle to improve cell recovery.

Potential impact:

Single-cell studies yield valuable information on naturally occurring or engineered variation not normally seen when measuring the average response from a cell population. The company believes that Cyto-Mine could reduce screening costs by more than ten-fold, while simplifying single cell studies

for scientists and clinicians worldwide, and accelerating the discovery of new enzymes, biopharmaceuticals, cell therapies and disease biomarkers.



ENDOZYME II GO

Endotoxin detection assay based on animal-free recombinant factor C

Produced by bioMérieux SA

The ENDOZYME II GO endotoxin detection assay enables endotoxin testing in pharmaceutical grade water, injectable drugs and other pharmaceutical products – and is particularly well suited to raw materials and final product testing. The assay uses the GOPLATE system, a 96-well microplate pre-filled with required standard curve and positive product control concentrations. It is ready-to-use and can enable significant reductions in handling-time

compared with conventional microplate-based endotoxin tests, which tend to require the preparation of standard dilutions and internal controls. The results of ENDOZYME II GO have been demonstrated by companies like Sanofi Pasteur (Marius et al, 2018).

Potential impact:

Animal-free recombinant factor C (rFC) technology, included in the European Pharmacopoeia since 2016, eliminates the need to harvest ecologically vulnerable horseshoe crabs (endangered in Asia, and declining and protected in the US). Their blood is used in most currently marketed tests for endotoxin detection. bioMérieux hopes that ENDOZYME II GO will accelerate the transition from animal-based LAL to sustainable rFC in the endotoxin testing market.



ESHMUNO CP-FT

Cation exchange (CEX) chromatography resin to remove monoclonal antibody aggregates

Produced by Merck KGaA

Eshmuno CP-FT is a cation-exchange (CEX) chromatography resin that uses a flow-through frontal chromatography mechanism to remove monoclonal antibody (mAb) aggregates. CEX bind/elute chromatography is typically used to remove aggregates from mAb feeds, but requires large volumes of resin to bind all of the mAb product. CEX flow-through frontal chromatography significantly reduces the volume of resin

required because the full capacity of the resin is used to bind the impurity.

Potential impact:

New tools are needed to increase the downstream purification efficiency of mAb therapeutics to match the increasing productivity of upstream processes. Aggregates are one of the most difficult impurities to remove from mAb feeds and traditionally require bind/elute chromatography processes that use large volumes of resin and buffer. Eshmuno CP-FT resin can reduce the volume of resin and buffer required to remove aggregates from a mAb feed by ten-fold relative to traditional bind/elute CEX resin, which can lead to significant cost savings as well as shorter processing time.





LINEARTWINSCAN

Automatic filter integrity tester for hot-air sterilization tunnels

*Produced by Bausch+Ströbel Maschinenfabrik
Ilshofen / InfraSolution*

LinearTwinScan is designed for use in combination with Bausch + Ströbel hot air sterilization tunnels, and was developed in collaboration with InfraSolution. To test filter integrity (ISO classification test and a filter integrity test), the filter is guided through the sterilizing tunnel on the tunnel conveyor belt in a precisely predetermined way. The operator makes all the necessary settings at the tunnel operating panel, and the progress of the test can also be tracked.

Potential impact:

Today, filter integrity tests – tests to assess the leak-tightness of the filters used in hot-air sterilization tunnels – are still performed manually. Test results are printed onto heat-sensitive paper and the printouts, which resemble small sales receipts, are glued onto the test report. Considering the high degree of automation now commonplace in the pharmaceutical sector, it is surprising that this is the best practice for the industry. With LinearTwinScan, measuring accuracy is no longer dependent on the meticulousness and experience of the operator. Test results are more reliable and reproducible, and data are also available in a digital form to meet relevant statutory requirements (21 CFR Part 1/GMP Annex 11).

Who's the Best?

We received dozens of entries for the 2018 Innovation Awards, spanning machine makers, to service providers, to software developers. Innovation is abundant in every corner of the

industry! We think the 16 winners here 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 showcased here. 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.



LYO-CHECK

A dedicated inspection system for lyophilized medicines

Produced by Antares Vision

Because the quality control inspection of products in lyophilized form poses unusual challenges, Antares Vision was awarded a European Commission Grant to develop and hone this new technology, which offers fully automated 100 percent inspection of lyophiles. The resulting LYO-CHECK machine is based on unique vision architecture, including dedicated software and optical layout.

Potential impact:

The LYO-CHECK inspection machine paves the way for an uptick in the use of lyophilization. Lyophilization of pharmaceuticals offers a number of advantages, including long-term storage (more than two years in some instances) even at room temperature, and enhanced protection from pollution. Lyophilized drugs also preserve the original product features, can be stored easily, and can be rapidly reconstituted for patient use.

MASTER DATA COLLABORATION TOOL

Blockchain-based tool to enhance supply chain transparency

Produced by Tjoapack Netherlands BV and Veratrak

Tjoapack and Veratrak have partnered to launch the Master Data Collaboration Tool – a live blockchain tool that can be used to create a more secure, transparent supply chain. The platform enables supply chain partners to more effectively collaborate on a number of documentation requirements to bring a drug to market. All document events (upload/new version/comments) are hashed and added to public blockchains, which provide an iron-clad audit trail of all documentation processes that cannot be tampered with.

Potential impact:

By enabling transparent collaboration across multiple pharma supply chain partners, the Master Data Collaboration tool helps reduce service lead times so that companies can better navigate their out-of-stock risks. Blockchain technology is already being explored as a solution to support track and trace programs that follow physical goods through the supply chain, but the technology can also be used to improve transparency through secure audit logs that are accessible for multiple parties. This can also facilitate collaboration across different companies, making the entire supply chain much more efficient, cutting redundancy and rework costs.





Who? What? Why?

What are The Medicine Maker Innovation Awards?

The Medicine Maker Innovation Awards, published every December, highlight the most groundbreaking drug development and manufacturing technologies released onto the market over the course of the year.

How are nominations received?

Nominations are collected via an online form at www.medicinemaker.com. Nominations are accepted from both users and vendors.

How are nominations judged?

All entries are evaluated carefully based on their potential impact on drug development and manufacture. The top technologies are selected to be showcased in The Medicine Maker.

Will the Awards be back in 2019?

Yes! Nominations for the 2019 Innovations Awards will open in Spring 2019. Keep your eyes on our website, www.themedicinemaker.com.

MICROCELL VIAL FILLER

Robotic, aseptic filling machine for personalized medicines, clinical trials and product development

Produced by Vanrx Pharmsystems

This system stands out for targeting cell therapies and other personalized medicines, and focuses on agility and sterility assurance. It is a gloveless robotic isolator that the company claims allows for the production of at least four personalized therapies in an 8-hour shift. The system has already won numerous awards, including the Interphex 2018 “Best in Show” award.

Potential impact:

The Microcell can help with the safe and rapid scale-out of manufacturing for personalized medicines, including cell and gene therapies and immuno-oncology products. The standard design can be built quickly, enabling companies to add more validated capacity in months, rather than years. Robotic automation and single-use product contact materials eliminate the risks of manual filling and cross-contamination, respectively. All of these aspects will contribute to the cost of goods for personalized therapies being significantly reduced.



NOVATRACK

Blockchain and serialization solution incorporating AI for supply chain security and transparency

Produced by Adents

NovaTrack incorporates blockchain, artificial intelligence, Internet of things, and serialization functionalities to provide a highly secure solution that provides transparency and enhanced control throughout the distribution chain – no matter how complex. The technology was developed in partnership with Microsoft and uses the Microsoft Azure Intelligent Cloud

platform to provide real-time performance, high scalability and business-driven data privacy.

Potential impact:

Blockchain is garnering increased attention throughout the pharma industry because it allows different supply chain partners to exchange information in a very secure and tamper-proof way. Track and trace legislation has created numerous challenges for pharma in terms of data sharing throughout supply chains.

NovaTrack was created to better secure entire supply chains via a multifaceted approach and help address the rise of counterfeit medicines. The technology allows users to collect and analyze data, and add embedded security features.

Q EXACTIVE UHMR HYBRID QUADRUPOLE-ORBITRAP MASS SPECTROMETER

A mass spectrometry platform that aims to expand our understanding of proteins

Produced by Thermo Fisher Scientific

This system has been designed to unlock a greater understanding of proteins and their interactions. The Q Exactive UHMR Hybrid Quadrupole-Orbitrap Mass Spectrometer is the first ultra-high mass range (UHMR) mass spectrometer (MS) to combine high m/z (mass to charge), MS^2 , and pseudo- MS^3 capabilities in a single platform. Delivering high sensitivity that minimizes sample volume, and ultra-high mass resolution at up to 80,000 m/z , the system can resolve the small differences in masses required to characterize intact biomolecular assemblies and other large molecule complexes. Ultra-high mass quadrupole selection and higher fragmentation efficiency allow improved native top-down analysis, which provides structural detail that cannot be seen with other methods.

Potential impact:

Native mass spectrometry is a powerful technique for studying the structure of large protein complexes, protein-protein, and protein-ligand interactions. It relies on maintaining a biomolecule's natural folded state and associated non-covalent interactions for MS analysis. Until now, technology limitations have prevented native MS from achieving its full potential. The Q Exactive UHMR Hybrid Quadrupole-Orbitrap Mass Spectrometer overcomes previous technology limitations and provides a workflow for protein structural analysis. The new system should give researchers the tool they need to gain a deeper understanding of protein function, disease mechanisms, potential drug targets and biotherapeutic compounds, and advance the study of structural biology.



ORBITRAP ID-X TRIBRID MASS SPECTROMETER

A mass spectrometer to improve small molecule identification and characterization

Produced by Thermo Fisher Scientific

The Orbitrap ID-X Tribrid Mass Spectrometer system combines quadrupole, Orbitrap and linear ion trap mass analyzer technology with novel automated data acquisition strategies and powerful structural analysis software processing tools. The combination provides a complete solution – from data acquisition to data analysis – and aims to significantly improve and accelerate the identification and characterization of small molecule compounds. Thermo Scientific Tribrid architecture, the AcquireX data acquisition tool, method editor templates and ready-to-use experimental parameters ensure efficient acquisition of high-quality data, even for non-expert users.

Potential impact:

Interpreting the mass spectra of unknown compounds remains challenging in pharma/biopharma. The Thermo Scientific Orbitrap ID-X Tribrid Mass Spectrometer aims to accelerate small molecule identification and characterization by automatically capturing the maximum possible information about small molecules and translating it into identification of chemical compounds. The system brings greater confidence to the analysis and identification of degradants, extractables, leachables, metabolites and other classes of compounds, and aids in metabolomics, lipidomics and the study of natural products.



SMART BLISTER PACK

An electronic tool to enhance medication adherence by clinical trial participants

Produced by Schreiner MediPharm

This electronic tool was developed to improve patient adherence during clinical trials. The Smart Blister Pack generates data from patients as they push tablets out of the blister pack via smart sensors, collecting information such as medication type, extraction type and the specific cavity. The data is stored in the smart packaging and transmitted to a database for analysis.

Potential impact:

Around 20 percent of patients do not adhere to medication, forcing clinical trial organizers to compensate for the resulting accuracy deficit by increasing patient populations by up to 60 percent. The Smart Blister Pack aims to transform patient clinical trial compliance by closely monitoring dosages and intake times. Additionally, the overall communication between patients and physicians will be improved, as doctors can send compliance reminders and dose adjustments to patients in real time.

SYRIO BIOPURE

Prefillable glass syringes for highly complex biologic drugs

Produced by SCHOTT AG, Pharmaceutical Systems

SCHOTT's syriQ BioPure prefillable glass syringes have been designed specifically for the biologic market to keep sensitive drugs stable, ease administration, and shorten time to market. Improved drug stability is reached via specialized manufacturing processes, which lead to ultra-low tungsten and low-adhesive residuals. The syringes are made of FIOLAX borosilicate glass and are available in over 48 pre-validated configurations.

Potential impact:

As well as ensuring drug stability of highly sensitive biotech drugs, syriQ BioPure supports key trends in healthcare, such as the move from hospital to homecare where patients self-administer therapies. The syringes have been designed to work with leading safety and autoinjector devices. A uniform silicone layer ensures full injection of the drug and smooth gliding performance to make the administration process more comfortable for the patient.



Words of a Winner

Earlier this year, readers voted SGS's H3N2 challenge virus as their top technology of 2017. Influenza has been an enemy of humanity for over a thousand years and its power is often underestimated. Challenge agents, used to induce a physiological response to test vaccines and treatments, can be an invaluable tool to help vaccine manufacturers keep up with this ever-changing virus – and, therefore, better protect patients. You can read the full story behind this innovation at <http://tmm.txp.to/0618/challengevirus>. We catch up with Adrian Wildfire, Project Director – Infectious Diseases/Viral Challenge Unit at SGS Life Sciences.

How has the industry reacted to the challenge agent over the past year?

We have seen a confirmation in commercial trials using our A/Belgium H3N2 influenza challenge agent of our original characterization study results, with excellent attack rates (>90 percent at a titer of 106) and consistent shedding in commercial trials. We have had positive comments from many sources in the industry and I really think we are making a difference with the work we have undertaken.

The H3N2 agent we made is now being trialed in intramuscular and intranasal vaccine trials, and we have firm data on performance with both monoclonal antibody therapies and novel small molecules. As the current clades of H3N2 are the real “bad boys in the playground”, improving serological and mucosal responses to H3N2 is essential if we are to protect pediatric populations and the elderly from serious illness and reduce hospitalization rates. H3N2 has changed its viral profile (HA/NA attachment strategy) radically in recent times and has not shown the antigenic stability of H1N1. We are working with academic centers, such as Imperial College London, to look into disease progression and markers – I hope this may advance our knowledge of the differences between H1 and H3 in promoting illness.

What was the most memorable moment of the project?

I think getting the first animal data was a great

moment. We knew then that the agent worked, that it had a very high attack rate and that non-attenuated strains did not induce severe disease or lower lung issues. It also gave us the confidence that we could manufacture GMP agents that retained fidelity or homology to type despite (in some cases) some pretty onerous regulatory requirements.

What other innovations are SGS now working on in the area of challenge agents?

We have a new respiratory syncytial virus challenge strain (WT RSV A (RSV-NICA) in manufacture right now. Again, animal data from the first batch looks very promising with 100 percent attack rates and typical symptomologies in cotton rats. I think this may offer a better alternative than currently available strains as it can be inoculated at titers more typical of natural transmission than like-agents.

Any other exciting company news?

SGS has an exciting malaria challenge project in the offing. Work has commenced on the implementation and operational side and I hope we can share more news in the New Year! SGS is also looking to work with a new US academic group and, here again, plans are relatively far advanced. All this plays in well to our expansion strategy and we are looking to increase both capacity and expertise in all challenge areas through inward investment and interaction with fantastic consortiums, like HIC-VAC and Bactovac among others. On a personal note, I have to thank both my managerial and operational teams for supporting these endeavors – sometimes you have to take calculated risks in clinical research, and their help and advice has been invaluable to achieving the successes we now share as a company.



ÜBERCELLFLEX

Modular cleanroom infrastructure for critical therapy manufacture

Produced by G-CON and IPS

G-CON is well known for its PODs – prefabricated cleanrooms that are readily deployable, mobile, flexible and scalable. Since then, in partnership with IPS, the company has launched the iCON turnkey facility platform for mAb manufacturing. Through iCON, the company now offers ÜBERcellFLEX PODs for cell therapy processing. They are available in 12 ft and 24 ft wide POD configurations. Multiple units can be installed to scale up/out from phase 1 clinical production to commercial manufacturing and serve the needs of thousands of CAR-T patients per year.

Potential impact:

The POD cleanroom units are unique from traditional cleanroom structures due to their ease of scalability, mobility and the ability to repurpose PODs once the production process reaches the end of its lifecycle. There is a major need in the cell and gene therapy space for standardized solutions. PODs are ready to order, in either open or closed-processing format, with little to no engineering time – fabrication begins almost immediately after user requirements specification alignment.

ZYDIS ULTRA COATING TECHNOLOGY

Taste-masking technology to deliver higher drug loading for orally dissolving tablets

Produced by Catalent Pharma Solutions

Zydis Ultra technology allows API particles to be coated within the Zydis ODT dosage form with a very thin (tens of microns) polymer. This coating is effective in taste masking the API without impacting oral disintegration time or its subsequent gastrointestinal dissolution performance. The coating technology uses acoustic mixing to bombard particles of the API with a micronized polymer. The energy produced increases the temperature of the API and polymer, allowing the polymer to form the coating over the API.

Potential impact:

ODT technologies can help boost patient compliance – particularly in pediatric and geriatric populations where swallowing conventional tablets can be a problem. There are numerous products on the market that use ODT technology, but challenges in formulation exist where APIs have a bitter taste, or may burn and irritate the mouth. There are also limitations as to the API concentrations available within each dose. The increased drug loading possible with Zydis Ultra allows ODT platform technology to be expanded to many more compounds.



Isolation

Expansion

Harvest

Formulation

Cryopreservation

Banking

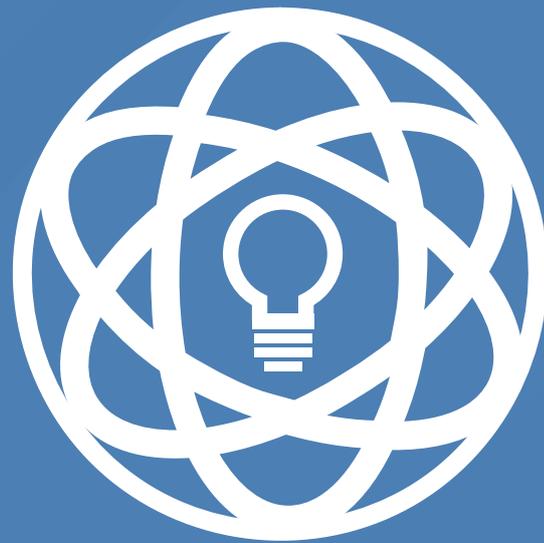


Helping your cell therapies succeed through our reach and resources.

Every step of the way,
it's personal.

Remove operational barriers to scale-up and scale-out by coordinating and automating your workflow. GE Cell Therapy Solutions' unique combination of automated instrumentation, reliable reagents, and consultative support accelerates your efforts from cell recovery to reformulation so you can pursue personalized medicine with lower risk and greater efficiency.





THE INNOVATORS 2018

Whether better ensuring patient safety, improving process efficiency, or just making life in the lab or facility easier – meet the companies advancing pharmaceutical development and manufacture.

GRANUCON – LCF 5 CONTINUOUS DRYER

Faster thanks to defined retention time distribution



Lödige has rounded off its product portfolio for continuous granulation with a new dryer: the LCF 5 is distinguished by a defined retention time of the product inside the machine. This enables shorter processing times to be achieved in production. With the LCF 5, CoriMix® CM 5 laboratory ringlayer mixer and customized dosing technology, Lödige now offers a complete continuous GRANUCON granulation line.

The LCF 5 dryer is based on the fluid bed process in which the material is dried in the fluid bed by convection. The drying

air is heated prior to entry into the fluid bed processor and evenly distributed through the special sieve tray of the product container. The current holds the product in suspension and fluidizes it. This guarantees excellent heat transfer and drying values while handling the product gently. With a new design Lödige has achieved a defined, narrow retention time in the new dryer of the GRANUCON line compared to conventional devices. The fluid bed dryer is designed for throughputs of 5 to 30 kg/h and product moisture levels of up to 20%.



THE NEXT GENERATION OF GLASS AND POLYMER PRIMARY PACKAGING

Primary packaging solutions that meet the needs of 21st century drugs and drug delivery devices

The next generation of vials concept is SCHOTT's modular approach, which offers pharma companies the opportunity to combine features depending on their needs. The vials are made of FIOLAX® CHR borosilicate glass tubing, featuring a controlled hydrolytic resistance. A superior extractables and leachables profile is achieved through the right converting process. The vials are manufactured using the company's validated, delamination-controlled production process to ensure full control of delamination. As the interior surface will remain untouched in its known borosilicate Type-I form, pharma companies do not need to worry about lengthy re-registration processes.

Moreover, the offering will also include features to improve the total cost of ownership (TCO) of pharma companies. This is achieved through more efficient processing on fill and finish lines. More concretely, it covers a flawless glass

quality from tube to container by optimized processes, which increase the strength of the vial. This is further enhanced by improving the dimensions for a perfectly shaped geometry and ultimately increased filling line yields. Lastly, due to post process of the outer surface of the vial, the coefficient of friction is reduced. The low-friction outer surface, in return, reduces any sticking or climbing effect on the filling lines to ensure smoother line operations.

Besides the next generation of vials, SCHOTT also leverages its extensive expertise in manufacturing containers out of cyclic olefin copolymer (COC) to offer manufacturers the ability to co-create a COC container around an existing device. As so far the drug delivery devices had to be built around the pharmaceutical packaging containers that are currently on the market, the device development was restricted in terms of design. Now, by co-developing a container made out of COC, the needs of the drug product, filling process and drug administration are met without compromising on the device design. The joint project is based on a four-stage sampling process to improve the time-to-market for the customer while also reducing financial risks. This enables manufacturers, for example, to reduce the size of the device for a more patient-centered device in a discrete look.

www.schott.com/pharma



KLEPTOSE® BIOPHARMA HYDROXYPROPYL -BETA-CYCLODEXTRIN

Leading the way in biologic drug formulations through innovation in protein stabilization

For biopharmaceutical formulators, the complexity and natural propensity of proteins to aggregate pose a real challenge at every stage of development. As a pioneer in the industrial development of hydroxypropyl- β -cyclodextrin and polyols, Roquette provides stabilization solutions for biologic drug development.

Our latest innovation, KLEPTOSE® BioPharma HPB & HP (hydroxypropyl- β -cyclodextrin) for protein stabilization, brings established excipients for small molecule applications to the biopharma formulation community by offering plant derived, multi-compendial grade formulation excipients and cell culture media components of the highest quality that are low endotoxin.

These products are supported by a vertically integrated and fiber-free supply chain, produced in a state-of-the-art facility (US FDA and ICH Q7 GMP compliant) with a tightly controlled process delivering highly reproducible and defined material, with reduced batch-to-batch variability.

Anchored by technical expertise, Roquette is a premier solutions partner for improving stability of therapeutic proteins. To support innovation, we've recently expanded our R&D and Customer Technical Service teams to Singapore's Biopolis international R&D center, where our experts partner with customers on new innovations and help solve existing formulation challenges.



MISSION DRIVEN ARCHITECTURE

iCON – Standardized facility methodologies to deliver innovation and realize a targeted mission

Since the advent of the human genome, the pharmaceutical industry has seen prolific scientific growth as new therapies are being developed; some therapies treat conditions formerly untreatable, while others have the potential to reduce the contraction of serious disease or even cure cancer. With lives sometimes literally at stake, our clients and their patients need a construction delivery solution that not only defers financial risk as long as possible, but rapidly skips to the end when drug efficacy confidence is high. Regardless of all the drug approval and regulatory requirements, we need to complete the mission of getting critical medicines and innovative therapies to patients sooner.

It is with this in mind that we have begun to compare the strict requirements of the pharmaceutical industry with the geographic strengths of the design and construction business; we have charted a course towards a solution that couples flexibility, mobility and rapid deployment into a turnkey IPD solution. We are combining pre-engineering, standardization and the strength of local craft labor with non-linear thinking and factory fabrication to deliver cGMP facility projects faster and more predictably.

Harnessing the power of concurrent construction, our iCON™ facilities are prefabricated at centers of excellence, allowing rapid

deployment of new facilities throughout the world. The platform design gives manufacturers the flexibility to migrate between multiple clinical manufacturing suites to a commercial production facility or anywhere in between.

For future molecules whose processes we cannot currently anticipate, the facility includes cleanroom technology which enables clients to remove single to multiple suites and utilize technology to reconfigure a facility instead of mothballing, demolishing and/or performing lengthy renovations on it with each new process.

Our goal with the iCON™ hybrid modular solution is to provide a more flexible and predictable outcome on EPCMV projects where quality, speed and getting critical products to patients are the first and foremost priorities.





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

In the past, biopharma companies were struggling with various risk factors which kept them from implementing single-use solutions.

With our solid single-use foundation for biomanufacturing processes we are solving all of these challenges simultaneously. Our fully integrated single-use platform connects an exclusive approach in biocompatibility, state-of-the-art integrity control and testing as well as a unique automation platform and supply network.

This strategy provides flexibility and acceleration which leads to a cost-effective process that ensures the quality of your biologics and enhances patient safety.

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Business

Economic drivers
Emerging trends
Business strategies



44-47

Always the Bridesmaid

The pharma industry and research community understands the importance of neglected diseases, but the field is still not receiving the attention it deserves.



Always the Bridesmaid...

Although research and development for neglected diseases now commands a significant amount of attention, a new financial modeling tool shows that there is still a major funding gap.

By Gavin Yamey

The recent progress in global health has been extraordinary. To give just one example, spurred on by the Millennium Development Goals, the global health community managed to cut the global child mortality rate by over half during 1990 to 2015. However, we are now in an even more ambitious era. The level of ambition is reflected in the United Nation's Sustainable Development Goals (SDGs), which include the target of ending "the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases" and ending

"preventable deaths of newborns and children under 5 years of age" by 2030. Achieving these zero targets will almost certainly be impossible unless we step up our investments in neglected disease R&D to develop new, game-changing technologies. There is no credible empirical research showing that the world can reach these zero targets for global health with today's technologies alone.

Scaling up investments in neglected disease product development is a responsibility for everyone in the global

health community across the public, philanthropic, and private sectors – including pharma companies. Of the many barriers to such scale-up, a major one is the lack of consolidated information about which product candidates (drugs, vaccines, diagnostics, etc) are currently in the pipeline and at what stage, the estimated costs to move these candidates through the pipeline, and the likely product launches. If such information were more readily available it would highlight gaps in the pipeline – i.e., which diseases have no or few products under development – and enable investors and advocates to more easily drive change by targeting their investment decisions. What we ultimately need is an open access platform that has complete information on the pipeline. Such a platform would be highly valuable to public, philanthropic, and private health investors, allowing them to focus their funding on the areas of greatest need.

At Duke University's Center for Policy Impact in Global Health in the US, we are trying to put the spotlight on the need to finance R&D for neglected global health conditions. Recently, we conducted a study that aimed to shed light on the pipeline process (1). We looked at current candidates in the R&D pipeline, including vaccines, drugs, diagnostics, vector control products, contraceptives and multipurpose prevention technologies, across 35 neglected diseases. To estimate the cost of pushing these candidate products through the pipeline, we used a new, user-friendly financial modeling tool, Portfolio-to-Impact (P2I). P2I is a custom-built, public costing model developed by the WHO's TDR (the Special Programme for Research and Training in Tropical Diseases). The tool can estimate both the funding required to take candidate products from preclinical phases to launch, and

the likely launches that would result. The tool shows us where the pipeline is most robust and where the real gaps are – crucial information if we, as an international health community, want to give a boost to the development of products available for the treatment, prevention and control of neglected diseases.

“I feel that the wider research community for neglected diseases has been left out of the loop by the pharma and health research industries.”

Enter the void

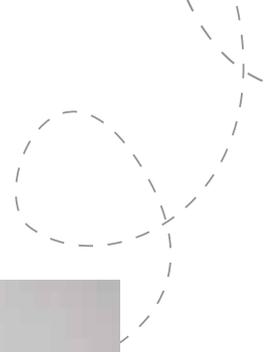
We initially identified 685 neglected disease product candidates as of August 31, 2017, of which 538 candidates met inclusion criteria for input into the P2I model. Of these 538 candidates, three diseases dominated the product pipeline process: HIV, malaria and TB. Specifically, they made up 57 percent of product candidates in the development pipeline, which reflects the fact they received around 70 percent of all funding for neglected disease product development. Certainly, these therapeutic areas are crucial as they contribute to an enormous number of deaths, but there are many other high-burden diseases that require attention,

such as hookworm, leprosy, lymphatic filariasis, and giardiasis. Many of these just had one or two product candidates under development (and we all know the rough odds of such a small number of candidates leading to a commercialized product). For hookworm, an estimated 450 million people are infected worldwide; how can we ever hope to control the burden if it only receives 0.001 percent of total R&D funding? Our study found only two candidate products for hookworm in the pipeline.

The P2I tool estimated that it would cost around \$16.3 billion to move these 538 candidates through the drug pipeline and estimated that it would result in about 128 product launches. Three-quarters of the costs incurred would be in the first five years. Around 40 percent of these launches would be diagnostics for HIV, malaria and TB – reflecting the higher probability of success for diagnostics in general compared with other product types.

Unfortunately, our study also suggests that we are unlikely to see launches by 2030 (the target year for SDGs) of 18 critically needed technologies: highly efficacious vaccines against HIV, TB, malaria, and hepatitis C (such vaccines are technologically difficult to develop and the success rates are low); a combined vaccine against multiple diarrheal diseases; a complex new chemical entity for TB; and new chemical entities for twelve neglected tropical diseases: Buruli ulcer, Chagas disease, dengue, human African trypanosomiasis, hookworm, leishmaniasis, leprosy, lymphatic filariasis, onchocerciasis, schistosomiasis, trachoma, and trichuriasis.

And we are also facing a funding void. The P2I model estimates that an additional cost ranging from \$13.6 billion to \$21.8 billion (depending on product complexity) would be required to launch these missing 18 candidates.

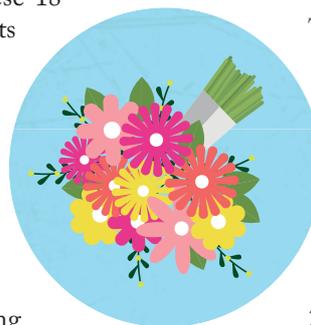


“Our study also suggests that we are unlikely to see launches of 18 critically needed technologies by 2030.”

Of these additional costs, about \$10.3-16.6 billion would need to be spent in the first five years (an annualized average of \$2-3.3 billion). Thus, overall, in the

first five years, total estimated costs to move all current candidates through the pipeline and develop these 18 prioritized missing products would be around \$4.5-5.8 billion per year. The annual G-FINDER surveys have shown that annual spending on neglected disease product development since 2008 has been around \$3 billion (2), suggesting that the annual funding gap is at least \$1.5-2.8 billion short. This figure is likely to be an under-estimate, as our model only looks at advanced pre-clinical to phase III costs, and does not include many other R&D costs, such as

early preclinical development, regulatory review and marketing authorization.



To action!

The pharma industry is significantly under-investing in neglected disease R&D. Out of the \$3.2 billion dollars invested in neglected disease product development in 2016, around 64 percent came from the public sector, 21 percent from the philanthropic sector, and just 15 percent from industry. In other words, total industry investment was just \$497 million in 2016. Companies can and must do

better. The health, social, and economic returns of investing in global health R&D are enormous, representing some of the largest returns in all of global development. As one example of how huge the returns can be, consider the development of the polio vaccine. The initial development cost was roughly \$26 million, and since routine vaccination was introduced, treatment cost savings have generated a net benefit of around \$180 million in the US alone (3). This is an astonishing rate of return, not to mention the impact on global health and wellbeing.

I feel that the wider research community for neglected diseases has been left out of the loop by the pharma and health research industries. In particular, much of the information about neglected disease candidates that

are at the preclinical research phase, and company information on product development costs, is under lock and key due to propriety interests and non-disclosure agreements. If an attitude of openness and transparency were fostered in the health research community, I think we would be better positioned to make a difference. If industry was more willing to share more information on its own neglected disease portfolio, we would be able to make more accurate estimations about the cost of moving candidates through the pipeline and the likely launches. I'd love to see other interested parties, including pharmaceutical companies, exploring tools like P2I to see how they can adapt it to create their own scenarios. And importantly, we should all be sharing the results so that we can inform the

global healthcare community and devise new processes for supporting R&D for neglected diseases.

Garvin Yamey is Professor of the Practice of Global Health and Public Policy, Director, Center for Policy Impact in Global Health, and Associate Director for Policy at the Duke Global Health Institute, US.

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News Flash

Biotage® Selekt has arrived

More productive, greener purifications

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Our new purification platform, Biotage® Selekt, utilises a host of ease-of-use features and a brand new modern user interface all packaged within the smallest flash system on the market.

Our new Biotage® Sfär spherical silica columns give unrivalled performance, while reducing solvent consumption, making for faster, greener purifications.

Visit our website to learn more about how Biotage® Selekt can take your laboratory to the next level in purification productivity.

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Biotage®





For Continuous Supply, Be Transparent

Single-source chromatography resin leads to requirements for supply security. Merck explains views and solutions.

With Nina Weis and Matthäus Braun

Merck's chromatography business has a long history—it was the first manufacturer of silica products for chromatography worldwide, starting one year after the discovery of the chromatography principle in 1903. Since then, the company has filed more than 50 patent families for process chromatography around the globe and offers a huge variety of chromatography products, including affinity chromatography resins, ion exchange resins, reversed phase media, membrane adsorbers and also pre-packed columns.

An important focus for Merck is ensuring security of supply for customers. "Because of the unique product characteristics and performance, as well as the complexity and cost of qualifications, chromatography resins are often sourced from a single supplier. A chromatography resin can impact the drug product's quality, safety and efficacy – and the effect can vary when switching to a resin from a different supplier. It can take years to replace a chromatography resin in an existing biomanufacturing process. Because of this, supply and production shortages have a huge impact on biopharma customers, which is why supply security must be a priority," explains Nina Weis. Responsible for managing Merck's near and long-term marketing strategy for ion exchange chromatography products, Weis has a strong focus on driving customer satisfaction.



According to Weis, supply disruption can easily equate to more than one million euros per day in lost revenue for blockbuster molecules, and it can potentially prevent patients from receiving essential medicines. "Chromatography supplies are essential for biopharma production. It is not sufficient for suppliers to focus only on delivering orders on time; it is also necessary to look to the future to better handle variations and minimize the impact of any unexpected events. In summary, long-term demand and capacity planning is crucial," says Weis.

Planning for all occasions

At Merck, demand planning and forecasting is a collaborative process with commercial and strategic marketing. Demands can fluctuate; low demand could result in a facility being under-utilized; however, high demand can stretch a manufacturing plant, leading to bottlenecks and supply disruptions. Therefore, it's necessary for demand planning to partner with capacity planning to review and discuss potential high-growth scenarios.

"Merck has a robust sales and operating planning (S&OP) process, which includes a monthly review of demand with commercial to understand our short and mid-term (0-18 months) customer requirements, and when orders will be placed," says Weis. "We also have a long-range plan for our business (3-5 years) in which we take into consideration market dynamics and product lifecycle. Twice per year, a plan is

provided to supply chain operations for capacity planning, future investments, resources, supply planning and more."

Prepare for the black swan

Of course, no matter how intelligently you plan your demand and capacity, your information will never completely reflect future needs. Uncertainty must always be considered – for the short-, mid- and long-term. There can also be unexpected catastrophes, from natural disasters, to changes affecting raw materials, to breakdowns in equipment that affect capacity.

Matthäus Braun is Site Director for Merck's Altdorf, Switzerland site, which produces chromatography resins, among other products. He says that the importance of continued supply is something Merck understands well since it is a biopharma manufacturer, as well as being a supplier business. "I like to say that it is in our DNA to look at supply risks and business continuity," says Braun. "We apply a holistic approach in the evaluation of any potential supply risks. For raw materials, for example, our business continuity plans involve supplier quality risk management, supply qualification, and established, long-term relationships with our key suppliers. Good relationships and trust are key for mitigating supply chain risk. We also have plans in place for other scenarios, such as breakdown of installations, or other unexpected events."

Merck's processes for business continuity follow pre-defined, formally documented






protocols that involve identifying a risk, determining and implementing an appropriate risk mitigation, which could be increasing safety stock of raw materials or qualifying a second source. Disaster recovery is also included in Merck's business continuity plans. The Altdorf site is not located in an area prone to major natural disasters and the environment is quite stable, but Braun says that it is still important to demonstrate to customers that the company has assessed the risks and has structured plans in place to reduce any recovery timelines, should anything happen. Braun says, "Our integrated supply chain operations organization has other sites in which we manufacture chromatography products and have subject matter expertise."

"It's really important to stay ahead of customers and market demand," Weis says. "We watch industry trends very carefully and listen to what our customers are telling us; and we have invested steadily in our manufacturing capabilities to expand

capacity and increase manufacturing standards according to the requirements of the biopharma industry. We have a large, state-of-the-art manufacturing network that produces our resins and membranes."

"Recently, we implemented a new production line in Altdorf to help us adjust to increased demand," adds Braun. "But we have the internal capacity to revert back to the previous production line if there is an issue with the new line. With everything we do, we also consider the 'black swan' situation and what might happen to production. It is important to have defined recovery plans and timelines."

Everybody wins

Whatever happens in the supply chain, both Weis and Braun agree that collaboration and communication with customers is crucial. "First of all, you can't just sell products without true knowledge about what they are used for," says Weis. "You also need to understand what clinical phase your

customer is at – are they preparing to go into commercial manufacturing, for example? Are their demands suddenly going to increase? Transparency goes a long way to making sure we understand our customer's needs and can continue to supply our products at the right time, in the right quality. We also partner with our suppliers to ensure transparency and a true collaborative business approach – a win-win situation for both parties that can strengthen the supply chain."

Open, regular dialogue with customers also builds trust. Braun adds, "Customers need to be able to trust that their supplier has effective plans in place to make sure supply will not be interrupted. A good relationship is key. In Altdorf, customers really appreciated how we demonstrated product equivalence from the previous production line to the new line, and how we managed the change. We also have an excellent track record with audits – something that demonstrates how well we understand the needs of our customers."

Change Control: At the Heart of Business Continuity

By Katrin Jänicke, Marketing Operations Chromatography

Every change to our products creates risk for our customers: a change has the potential to affect drug product quality, safety or efficacy, as well as the process performance. If a change results in an update to a regulatory filing, this could have a negative impact on supply. At Merck, we are highly focused on minimizing the risk that changes can bring. To address this, we have developed robust and comprehensive change control strategy that ensure changes are controlled, managed and communicated stringently to sustain security of supply.

There are two different scenarios why changes can occur; i) change is initiated by the manufacturer of the chromatography product resulting from continuous improvement efforts. ii) change is initiated by the manufacturer's supplier, such as a new supplier or a new raw material. One key element of our change control strategy is to communicate changes to our customers as early as possible to give sufficient time to prepare and assess the impact – we are targeting at least six months for change notifications prior to implementation of very complex changes. To ease our customer's risk assessment for those changes, we provide comprehensive comparability studies and the option to order samples from different lots in case a customer decides to perform additional testing. We understand that qualifying a change requires considerable effort; therefore

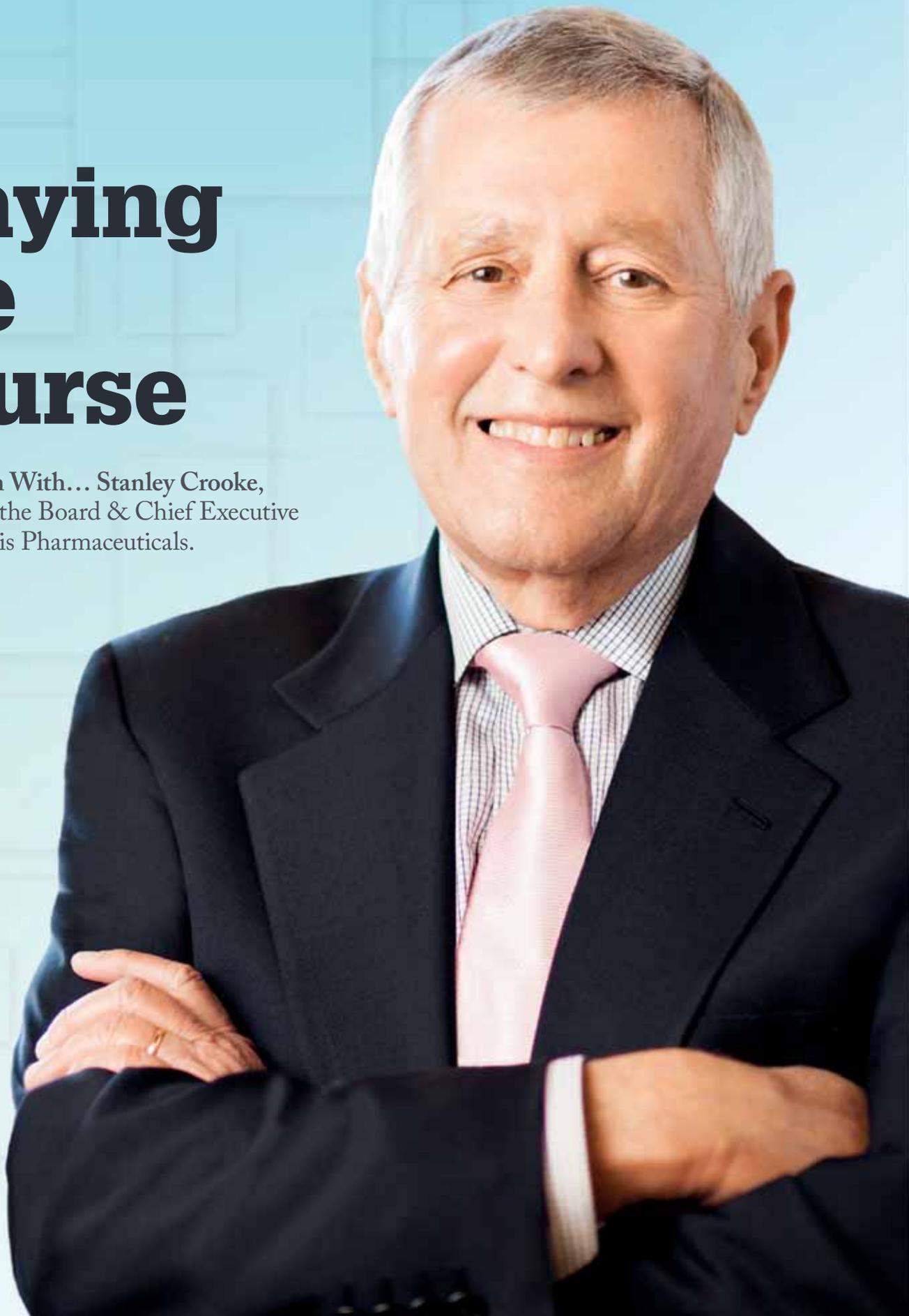
we try to find a good balance between continuous improvement and minimizing the number of changes. In addition, we're actively seeking the exchange with the industry. One example for this is the one-on-one exchange with customers where we present a specific change, and give the opportunity to ask questions and to provide feedback on how we can further improve our change control strategy. Another example is our involvement in industry consortia, such as the BioPhorum Operations Group (BPOG), where representatives from our company meet with other representatives from the biopharmaceutical industry to discuss and align on change notification needs and best practices.

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



Staying the Course

Sitting Down With... Stanley Crooke,
Chairman of the Board & Chief Executive
Officer at Ionis Pharmaceuticals.



Where does your passion for work stem from?

I've always loved being involved in the advancement of science and medicine; there is an immense sense of gratification in knowing that the hours spent in the lab, or running around a hospital, can result in life-changing results for patients.

Everything we do at Ionis is with the intention of bettering the lives of the hundreds of thousands of patients who use our products. It's impossible to put into words the thrill of receiving pictures and videos from patients, showing how well they have responded to one of our drugs.

From the inception of the company, I have always tried to foster a positive work culture. I've always believed in taking appropriate risks in an industry where saying "no" to innovative ideas is commonplace. Indeed, I believe in saying "yes" to ideas, to people, and to the notion that there may be a patient who could benefit from us taking an alternative approach. Nothing of value can ever be achieved without taking a step into the unknown.

How have your previous roles shaped who you are today?

A profound moment in my early career happened while I was still a resident at Baylor College of Medicine; a patient with disseminated testicular cancer was referred to the service I was on. He was 25, not much younger than myself, but he had a six-month death sentence... It was a harrowing experience, but it triggered my interest in the industry. Incredibly, the first company I worked for in the industry was Bristol-Myers, where I had the opportunity to build a cancer program.

I've been fortunate to have many formative moments in my career. In 1980, I was recruited by SmithKline to head up their R&D department. I was 35 at the time and the experience afforded me the opportunity to rebuild the organization. My successes and failures defined my experience at SmithKline and left me with

lots to learn from, particularly in regard to the technology being used in the industry.

Why did you found Ionis?

In the late 1980s, we were beginning to see a change in the industry. Gene therapies had captured the interest of many a company, and there were ideas being thrown around about the development of new platforms. But concurrently, we were also experiencing a decline in productivity. The space for new technologies was wide open and needed to be capitalized upon. It prompted me to found Ionis to pursue the technologies that I thought could bring great value to the industry.

When it comes to our technology, we're finally seeing the promise of these treatments being manifested. As the technology used continues to evolve, we're seeing vast improvements in the kinds of drugs in the pipeline. We currently have 45 drugs in the pipeline – which is one drug for every twelve employees at Ionis! We're all extremely excited to see how far we've come.

How did you rise to the challenge of being CEO?

I've actually run small businesses throughout my career. In many ways, managing a small drug store isn't dissimilar to running a large organization; you have to apply the same basic principles. But it's important to remember that in business you're competing against other human beings but when developing a new drug you are competing against evolution which, in my opinion, is a much harder task.

I've had to overcome the negativity of naysayers in the industry and explain why our products are important to the Wall Street-types who are evaluating the progress of the company. Scepticism is part and parcel of this industry, as most of the things you try end up failing – and perseverance in the face of criticism is not always easy. Embarking on this journey has been surprisingly emotional, but we have learnt to roll with the punches.

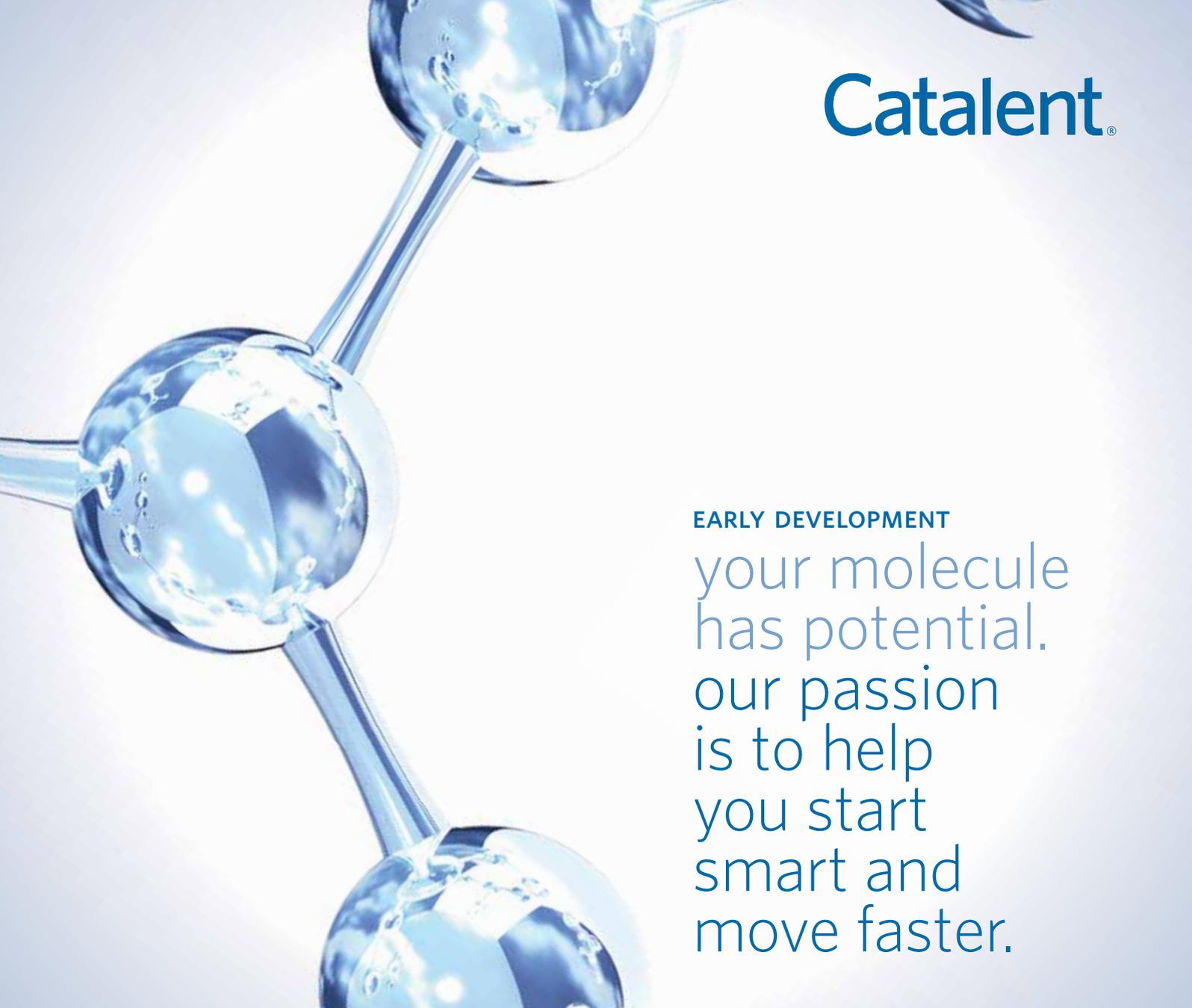
"Nothing of value can ever be achieved without taking a step into the unknown."

What frustrations do you have with the industry?

The industry stands for a noble cause and there are many people who I admire in this space, but we could all do better. The days of "me too" drugs within a given category making money are over. I want to see innovative approaches and ideas embraced more. There is a limit to what can be achieved from the traditional approach to drug discovery and we need to improve the efficiency of the industry.

What advice would you give to others wanting to make a mark on the industry?

When the company was in its infancy, there were many others around with similar ideas but they changed directions and moved into other areas. I'm glad to say that we persevered and we have managed to create something beyond our own expectations. We don't have any lingering thoughts in the back of minds about what could have been, because we stuck to our guns through the difficult times. It is a massive challenge to get a drug approved, get shareholders on your side, and stay afloat when inevitable disappointments crop up. But my advice to anyone wanting to really make an impact in this industry, or any other, would be: stay the course. Maintain your discipline and remember that it is impossible to create something of value without hitting a few stumbling blocks.



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