JUNE 2017 # 31

the Medicine Maker

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Online this Month

What? The annual Medicine Maker Innovation Awards recognize the most exciting, commercial drug development and manufacturing technologies released onto the market over the course of the year.

Why? Innovation is crucial in any industry, but its impact is perhaps best felt in the pharma, medical and healthcare fields where it saves lives. When considering innovation in pharma, we should not forget the technologies, tools and services, and the vendors who tirelessly work to ensure that the pharma industry has everything it needs to develop groundbreaking new medicines. The Medicine Maker innovation Awards give vendors the opportunity to showcase their latest technologies.

How? To be eligible, the product must have been launched (or will be launched) between January 2017 and December 2017. The "product" can be equipment, software, instruments, technology or even a service relating to any area of drug development, manufacture and formulation. Enter using our nomination form: http://tmm.txp.to/innovation-form2017

When? Nominations will close on Friday 10 November. All eligible nominations will be put to a judging panel, who will select the top ten innovations to be highlighted in the December 2017 issue of The Medicine Maker. The overall winner will have the opportunity to share the developmental story behind their product in a 2018 issue of The Medicine Maker.

Questions? Email the editor, Stephanie Sutton: stephanie.sutton@texerepublishing.com

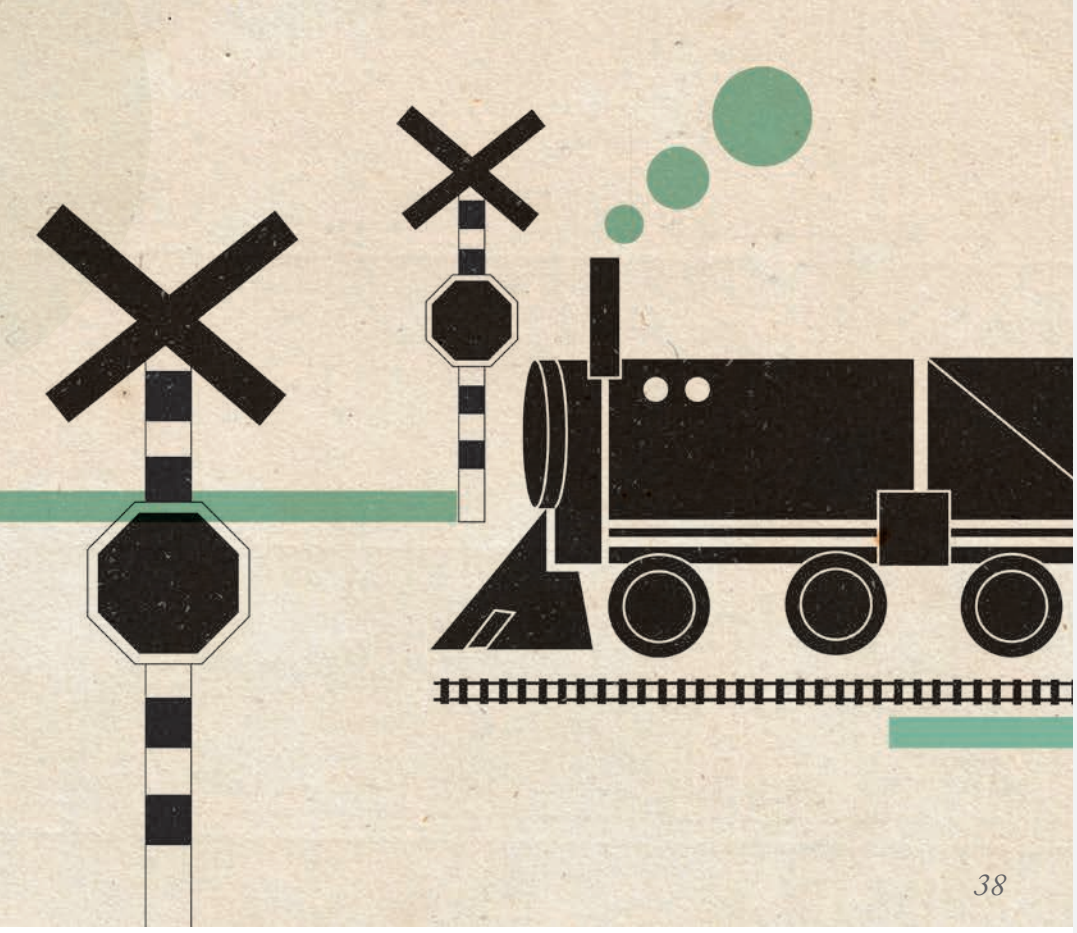
Contents

20

50

On The Cover

What potential does the chemically complex cannabis plant hold for drug discovery? Image courtesy of CMW Media.



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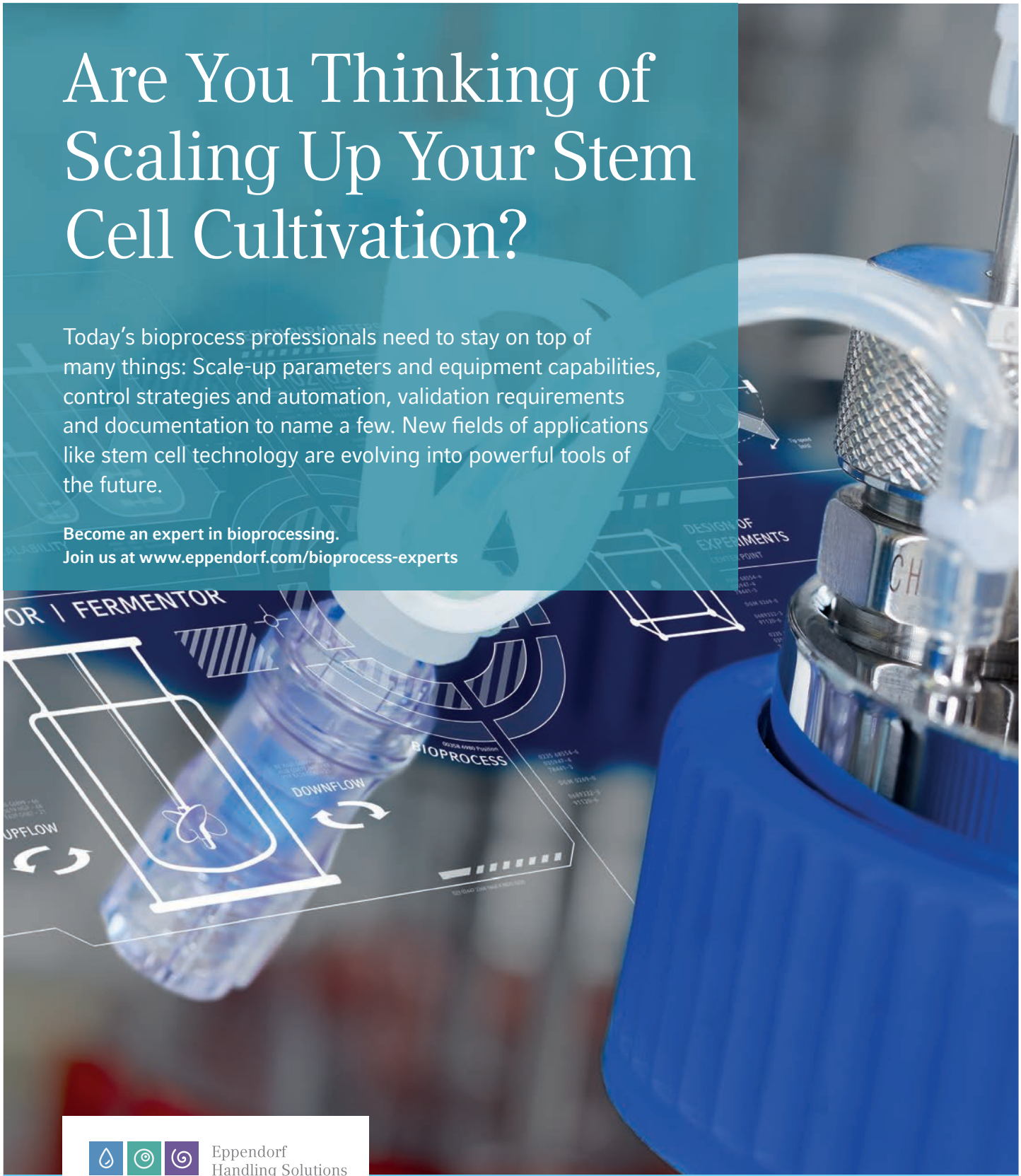

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Bringing Down the House

Pharma's guide to construction: plan facility, build facility, demolish facility (before use)...

Sanofi recently announced its intent to demolish a small-molecule plant in Montpellier in France. Demolishing an unneeded plant is nothing unusual – some facilities are simply too old or expensive to repair. But the Montpellier plant (named DI 50) is new – it was completed in 2012 and has never been used. Why? The times – and Sanofi's needs – have changed. The decision to build the plant was made in the early 2000s, and in recent years Sanofi has focused more on biologics than small-molecule drugs.

Attempts to sell or lease the facility have been unsuccessful and with property tax on the building estimated at one million euros per year (1), Sanofi had to take action. The equipment will be salvaged but the plant itself is likely to be demolished by the end of 2017. The whole scenario has been labeled as a huge waste by the French media, with some calling to have the building repurposed so that local universities can use it for training (2).

It's not the first time that a facility has run into issues shortly after construction – and it's unlikely to be the last. In the 2000s, Genentech constructed a biologics plant in Vacaville, California, but the plant was closed in 2010, once again because of shifting needs. In 2013, Genentech decided to resurrect the plant, but it needed a significant amount of work (and investment) to bring it up to date (3). The plant reopened in 2015 – and was the overall winner of ISPE's Facility of the Year awards in 2016. A happy ending.

Planning (bio)pharma capacity requires a skill that is impossible to fully master: predicting the future. Although analysts do their best to divine the demand that lies ahead, the process is more art than science – just like any other forecast; a 2016 survey of 50 pharmaceutical industry senior managers found that many companies had over- or underestimated demand for new drugs by up to 25 percent, with some being off by more than 50 percent (4).

For Sanofi, writing off a new facility and an investment of more than 107 million euros can't have been easy, but given 2016 revenues in excess of 33 billion euros (5), it's unlikely that too much sleep will be lost over the matter. But for the dozens of smaller companies that have got it wrong over the years? That's a different story.

Stephanie Sutton
Editor

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3. *S Sutton, "Facility Innovation by Design," The Medicine Maker, 12 (2016). http://bit.ly/2sA5yYx*
4. *Patheon, "Flexible Manufacturing Can Help Pharmaceutical Industry Avoid High Costs Of Inaccurate Demand Forecasts," (2016). Last accessed June 14, 2017. Available at: http://bit.ly/2ruOlv2.*
5. *Sanofi, "Q4 and Full Year 2016 Results," Last accessed June 14, 2017. Available at: http://bit.ly/2s00Phu.*

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

CLOUD with a Silver Lining

A new drug database is already helping to uncover novel combinations

When you think of a good weather forecast, you might picture a landscape without a cloud in the sky, but for a bright therapeutic forecast a CLOUD might be exactly what we need. Adding to the search for novel therapies, the Centre of Excellence for Medical Multimedia (CeMM) in Colorado Springs, US, has created a database of FDA-approved drug compounds that can be used to easily compare combinations of drugs: the CeMM Library of Unique Drugs – CLOUD for short.

"At first, we just bought commercially available collections, and used a bioinformatics approach to identify the best of several competing products. But at that stage, we realized that all commercially available drug collections – even when combined – lacked approved compounds for a significant number of target classes," says Stefan Kubicek, Head of the Proteomics and Metabolomics Facility at CeMM. "We decided to make our own reductionist collection that optimally represents all approved drugs regarding their molecular targets and chemical structures." The result is a highly condensed library of 308 compounds, which includes features that have been neglected in other libraries, such as the active metabolite of drugs administered as prodrugs.

Why the reductionist approach? "The collection of only 308 compounds is small enough for systematically testing all pairwise combinations," Kubicek explains. "Carrying out systematic combinatorial screens on the scale of,

for example, all compounds in the NIH Chemical Genomics Center collection, would easily overwhelm even the largest industrial screening infrastructures."

The downscaling of the task allowed CLOUD to be created in just a few simple steps:

1. Extract unique active pharmaceutical ingredients from the Drugs@FDA database.
2. Remove large macromolecules, molecules that don't operate via protein-ligand interactions, molecules that aren't used to treat diseases, and molecules that are only found in tropical regions.
3. Annotate the remaining drugs with their molecular targets, and group them by target class and chemical structure similarity.
4. Combine the list with the 34 drugs that have unknown targets alongside their 35 active forms of prodrugs.

The resulting 308 compounds encompass all FDA-approved chemical entities (including active forms) in a single screening plate. Other aspects of CLOUD creation were more complex. "While databases exist for chemical structures and targets of approved drugs, maximum human plasma concentrations are not systematically annotated and, for many compounds, there is high variability in the numbers reported in the literature," says Kubicek. "Another challenge was the physical assembly of the collection. Though the majority of these compounds are readily available, a subset was hard to obtain."

Labs at the CeMM now use CLOUD for the setup and optimization of all their screens. One group has already discovered that a combination of flutamide and phenprocoumon modulates androgen receptor (AR) stability and re-sensitizes AR-mutant prostate cancer cells to flutamide, for example (1). "At concentrations where neither compound affected the viability of these cells, the combination efficiently killed the cancer cells," says Kubicek. "Based on the known use of the antiandrogen flutamide as a prostate cancer drug, we tested the combination in prostate cancer cells and found an even higher degree of synergy. Thus, we could describe the discovery and molecular characterization of a novel drug synergy that has the potential to clinically benefit patients with resistant prostate cancer."

The latest discovery showcases the potential of CLOUD – and Kubicek hopes that other screening centers around the world will adopt similar approaches. *WA*

Reference

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Nanofluidic PAT

Is continuous, real-time analysis of biologics during manufacturing on its way?

Applying quality control to living organisms is tricky at best – but also crucial: the quality of biopharmaceuticals has a clear impact on both safety and efficacy. And so quality assurance is typically conducted at the end of the (lengthy and costly) biomanufacturing process – but is that logical? "If the manufacturing system produces low-quality or abnormal biologics, it is hard to see whether the product quality and system operation are normal or not during the manufacturing process through conventional analytics systems," says Sunghee Ko, Postdoctoral Associate of Jongyoon Han's laboratory at the Massachusetts Institute of Technology. "Because of this, current quality measurements (for example, release analytics) can lead to money loss and a disruption of biologic supplies when manufacturing has problems."

The logical solution? Monitoring biologics during the manufacturing process. Han's lab has taken on the challenge and created a nanofluidic device that they plan to directly link to a bioreactor to monitor purity and bioactivity with high sensitivity, resolution, and speed. "This is one of the preferable monitoring methods to realize process analytical technology (PAT) defined by FDA, and allows us to respond rapidly if there is a change in bioreactor conditions that affects the quality," says Ko.

The device is based on a series of nanoscale filters – or, to be more precise, patterned nanochannel arrays of varying depths and protein electrical potentials – that separate molecules by size (from 14 – 200 kDa). The team's paper (1) demonstrated multiparameter quality monitoring of three 20µl biologic samples within 50 minutes, but also shared a prototype on-line sample-preparation system that could make at-line monitoring – and therefore real-time quality assurance of biologics – a reality. *WA*

Reference

1. *SH Ko et al., "Nanofluidic device for continuous multiparameter quality assurance of biologics", Nat Nanotechnol, [Epub ahead of print] (2017). PMID: 28530715.*

Leidenfrost Nanochemistry

Scientists fabricate anticancer nanoparticles by recreating deep sea volcano chemistry

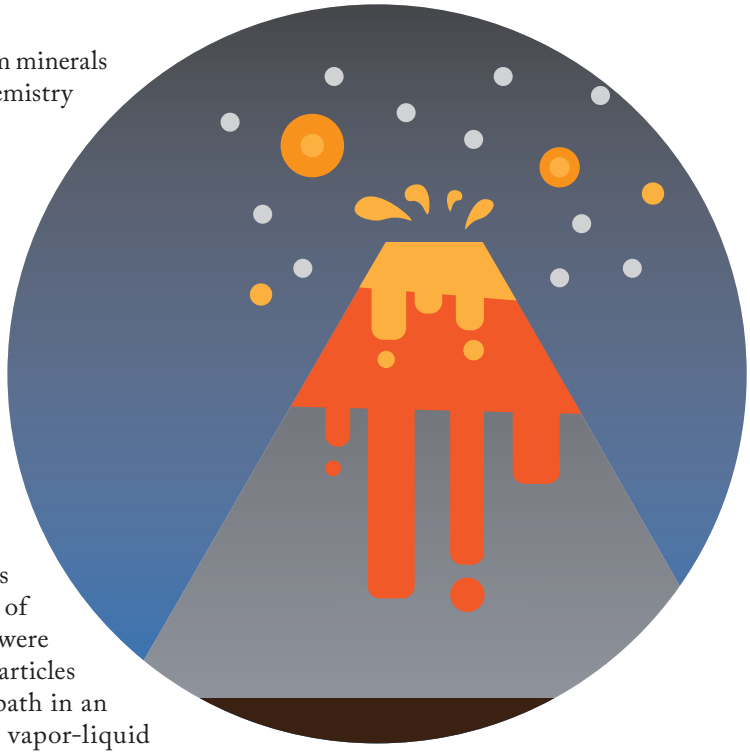
Current methods for fabricating nanoparticles, such as hydrothermal synthesis, laser ablation, or gel synthesis, all involve environmentally unfriendly surfactants, as well as expensive instrumentation. But what if fabrication could be achieved simply with a water bath and hot plate? Inspired by the way water dances on a hot pan – the Leidenfrost phenomenon – and similar chemistry that takes place in underwater volcanos, Mady Elbahri, Professor of Chemical Engineering at Aalto University, Finland, has developed an environmentally friendly means of producing ZnO_2 nanoparticles (1). What's more, Elbahri's team has also found that the nanoparticles can kill cancer cells. Here, he tells us more about Leidenfrost nanochemistry.

What inspired this work?

It started with the Leidenfrost phenomenon. When cooking in the kitchen, you may have noticed that when a water droplet touches the surface of a very hot pan, instead of evaporating, it moves and dances. I observed this phenomenon – the Leidenfrost phenomenon – in my kitchen a few years ago, and after contemplating the mechanisms behind it, I thought that it could potentially be useful for nanosynthesis. After some initial research, I introduced the novel concept of "Leidenfrost nanochemistry," which means synthesis of nanoparticles using the Leidenfrost effect. To scale up the process, we sought to recreate the way underwater volcanos form minerals through Leidenfrost chemistry using a hot water bath.

How does Leidenfrost nanochemistry work?

In the proximity of volcano gates, deep in the ocean, the dynamic chemistry taking place is unique in terms of self-regulation and openness to flow conservation, which enables simultaneous chemical synthesis and self-organization of minerals. Similarly, we were able to synthesize nanoparticles at the bottom of a hot bath in an overheated zone at a vapor-liquid interface. The particles then erupt towards the colder region of the liquid-air interface – making them increase in size. This physical separation allows us to tailor the size of the particles with an optimum monodispersity. Monodisperse nanoparticles show uniform properties and induce similar responses in the cells they interact with, which is important in terms of using them for therapeutic purposes.



How do ZnO_2 nanoparticles kill cancer cells?

I became interested in ZnO_2 nanoparticles after reading the work of Otto Heinrich Warburg, who won the Nobel Prize in 1931 for showing that cancer can be caused by lack of oxygen in cellular respiration. I theorized that peroxide nanoparticles, as a rich source of oxygen, would be able to kill cancer cells by delivering oxygen to cancer cells and inducing oxidative stress. The theory was tested in a series of experiments, which went well. Never before has the impact of ZnO_2 nanoparticles on the survival of cancer cells, as well as normal healthy cells, been studied. And the result? ZnO_2 nanoparticles have adverse effects on human cells, cancer suspension cells, and adherent tumour cells, depending strongly on the size of the particles and the cell physiology.

What comes next?

We plan to conduct further research to discover what size and dose of the nanoparticles works best for potentially combating cancer. We also hope to learn more about the mechanism involved in the cytotoxic effect of ZnO_2 particles on various cell types. We are also looking for investment so that we can further expand the range of applications for Leidenfrost nanochemistry.

Reference

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What Bad Rep?

Does pharma have a poor reputation? It's not nearly as bad as you might think...

An annual survey from the Reputation Institute has found that, contrary to the belief of many in the industry, pharma's reputation is "strong" – an improvement on the previous three years' "average/moderate" score (1). The study asked participants about a number of factors, including whether or not companies have a "positive influence on society" or "behave ethically." The survey found that 11 of the 17 companies analyzed had improved their reputation over the past year, with only two companies losing reputation. Here, we delve a little deeper into some of the figures from the report.

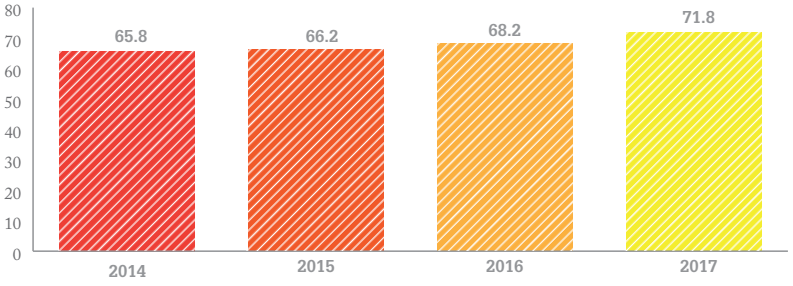
Reference

1. *Reputation Institute, Pharma RepTrak 2017, (2017). Available at: http://bit.ly/2swwEj6. Last accessed 13 June, 2017.*

Best and worst reputations in pharma

Company	*Rating*	*Development since 2016*
AbbVie	74.5	Up 5.3
Novo Nordisk	74	Up 3.8
Takeda Pharmaceutical	73.8	New
Roche	73.4	Up 3.7
Janssen Pharmaceuticals	72.5	No change
Gilead Sciences	72.4	New
Bayer	72.3	No change
MSD / Merck & Co	72.2	Down 1.7
Sanofi	72.0	Up 4.0
Eli Lilly	71.9	Up 4.1
Allergan	71.8	Up 3.4
Merck KGaA	71.6	Down 1.8
Bristol-Myers Squbb	70.5	Up 4.1
AstraZeneca	70.4	Up 3.1
Novartis	70.4	Up 3.4
GlaxoSmithKline	68.5	Up 2.0
Pfizer	68.4	Up 3.5

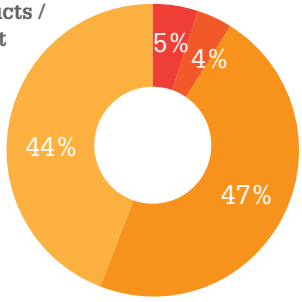
Pharma has a "strong" reputation for the first time



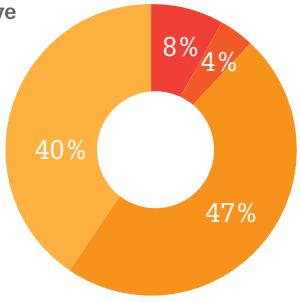
Note: The maximum possible score is 100

Average scores across companies

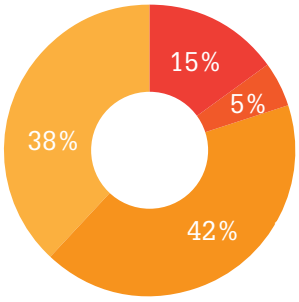
Offers products / services that are good value for money



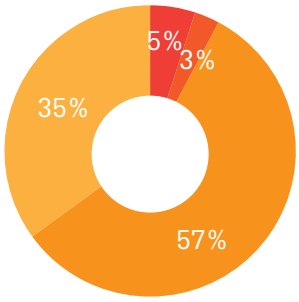
Has a positive influence on society



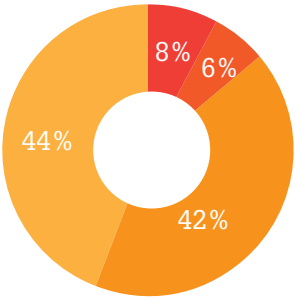
Behaves ethically



Commited to advances in treatments and cures



Sets prices fairly



Reputation of pharma industry by geography

Highest score

Lowest score

A Positive-Sum Game

Academics highlight the scale of post-market safety events – and the need to invest in pharmacovigilance

The job of a medicines regulator is a precarious balancing act. The primary concern has to be the safety of patients but, if the barriers to approval are too high, it can reduce the number of lifesaving therapies available to those patients. And that's where pharmacovigilance comes into play. By monitoring the effects of drugs post-approval, warning signs can be recognized and appropriate action taken, such as changing safety information or, in extreme cases, removing a drug from the market. Two recent studies highlight the importance of pharmacovigilance; the first looked at the total number of post-market safety events in the US over a period of 10 years (1), and the second analyzed the monetary cost associated with failing to invest in fully functional pharmacovigilance programs (2).

The scale of the issue

A collaborative team comprising six different institutions from the US and France analyzed the number of post-market safety events between 2001 and 2010 (1). Of the 222 novel therapeutics approved during this period, 32 percent were affected by a post-market safety event. Overall, there were 123 safety events, including three withdrawals, 61 boxed warnings, and 59 safety communications, during a mean follow up of 11.7 years.

The research team also found that post-market safety events were statistically more frequent among biologics and drugs used to treat psychiatric disease, as well as those receiving accelerated approval and those with near-regulatory deadline approval. Post-market safety events were less frequent among therapeutics approved with a regulatory review time of less than 200 days, which, according to the authors, suggests that some approval packages provide clearer evidence of safety – leading to fewer post-market safety events.

In the discussion, the authors argue that additional pre-market review may only delay approval without identifying therapeutics that pose future safety concerns. They advocate greater collaboration between the FDA and other stakeholders, as well as the sharing of pre-market clinical trial data.

The return on investment

What about the financial cost of failing to invest in pharmacovigilance? Researchers from Brigham and Women's Hospital looked into cases studies of three drugs – rofecoxib, cerovastatin, and troglitazone – and suggested that the early signals of safety hazards were not adequately recognized (2). The lack of vigilance resulted in continued exposure of a large number of patients to the drugs, when safer and effective alternative treatments were available.

The authors stated, "Earlier drug withdrawal made possible by active safety surveillance would most likely have resulted in savings in direct medical costs of $773-$884 million for rofecoxib, $3-$10 million for cerivastatin, and $38-$63 million for troglitazone in the US through the prevention of adverse events." They contrast the figures with the amount the FDA spends on population-based pharmacovigilance activities in the US – around $42.5 million – and concluded, "Our analyses demonstrate a pivotal and economically justifiable role for active pharmacovigilance in protecting the health of the public." *JS*

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1. *N S Downing et al., "Postmarket safety events among novel therapeutics approved by the US Food and Drug Administration between 2001 and 2010", 317, 1854-1863 (2017). PMID: 28492899.*
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Business-in-Brief

Free cancer drugs, mispackaged contraceptive pills, and antibiotic action... What's new for pharma in business?

Regulation

- Pfizer's drug palbociclib has been shown to increase progression-free survival of breast cancer for a median of 24.8 months when given in combination with letrozole (14.5-month median with only letrozole) (1). However, the UK's National Institute for Health and Care Excellence (NICE) decided in February that the pharma giant needed further clinical data before the drug would be made available on the National Health Service (NHS). While the drug is in regulatory limbo, Pfizer has decided to make the drug free to patients – ordinarily worth £79,560 (~US$ 102,000) for a full course.
- The FDA have requested that Endo Pharmaceuticals remove their drug Opana ER from the market because of the opioid crisis in the US – the first time the agency has made such a request. In a statement, FDA Commissioner Scott Gottlieb said, "We will continue to take regulatory steps when we see situations where an opioid product's risks outweigh its benefits, not only for its intended patient population but also in regard to its potential for misuse and abuse."
- The FDA, EMA, and Japanese PMDA have agreed to adopt a more unified approach to new antibiotics by aligning data requirements for certain aspects of the clinical development of new antibiotics. Each agency will be updating its respective guidance documents.

Manufacturing

- Perrigo has recalled a number of medicines already this year and is now voluntarily recalling certain bottles of its Option 2 emergency contraceptive levonorgestrel pills in the US and Canada because of a packaging problem – some containers may be missing the tablet blister strip and tablet.
- One lot of birth control pills (Mibelas 24 Fe) is also being recalled by Lupin Pharmaceuticals after an error led blisters to be rotated during the packaging process, resulting in some tablets being placed out of sequence – the first four days of therapy would have had four non-hormonal placebo tablets as opposed to the active tablets.

Research

- Merck Sharp & Dohme's fast-tracked pembrolizumab (Keytruda) has become the first FDA-approved cancer drug to treat tumors based on genetic information, rather than cancer location. The drug combats multiple cancers – skin, head and neck, urothelial bladder, non-small cell lung cancer, and more – that all stem from the same genetic abnormality.
- Researchers from the Ben-Gurion University of Negev, Israel, are developing a new amyotrophic lateral sclerosis drug, based on a previously FDA-approved drug – Roche's rituximab – which is currently used to treat autoimmune diseases.

For links to press releases and source material, visit the online version of the article at http://tmm.txp.to/0617/business

Reference

1. *RS Finn et al., "Palbociclib and letrozole in advanced breast cancer", N Engl J Med, 375, 1925–1936 (2016). PMID: 27959613.*

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

When Experiments Go Wrong

Laboratory safety is a priority for all. We need to get better at sharing data on hazardous chemical reactions.

Carmen Nitsche is Business Development Consultant at The Pistoia Alliance, USA.

In February 2017, a PhD student at the University of Bristol in the UK was conducting a routine experiment. An unanticipated reaction created triacetone triperoxide – a highly explosive substance – and the emergency services were called to carry out a controlled explosion. Fortunately, no one was hurt, but the incident highlights how easy it is to unintentionally create a hazardous chemical or unwanted reaction, particularly in a research institution.

A chemical reaction doesn't have to create an explosion to be hazardous. Depending on the scale of the reaction, reagents can violently interact to shatter glassware, spew forth toxic gases or burst into flame. There are numerous books, databases and other resources available that outline reagent safety information, but what would be more beneficial is a searchable, freely available database on unintended reaction incidents and near-misses. Such practical information does exist of course – but it's often locked in internal silos, where it is difficult to find and share even within a company, much less across organizations (nobody likes to admit when an experiment has gone horribly wrong...).

As the life sciences industry relies on experimentation to develop new products, there is no way to eliminate risks entirely. However, the same negative incidents should never happen twice. Researchers need access to previously reported dangers. To this end, The Pistoia Alliance has recently developed the Chemical Safety Library Service. The service allows the research community to submit, store and share hazardous chemical reaction information.

The library has been seeded by members of The Pistoia Alliance, with a number of incidents from their archives. Members can add and share their chemistry reaction-related incidents and learnings – and the content is free to download and integrate for use with internal informatics systems, such as electronic lab notebooks or inventory systems. These systems can also be configured to alert scientists if there is a potential known safety risk before they carry out an experiment.

Since the majority of safety information falls in the precompetitive arena, sharing this kind of experience should be straightforward. Moreover, in cases that do involve proprietary components, the Chemical Safety

"Members can add and share their chemistry reaction-related incidents and learnings."

Library offers a function to convey these important safety learnings without revealing company intellectual property.

The Pistoia Alliance is a global not-for-profit organization that intends to help lower the barriers to innovation in life sciences R&D – and one of our key focuses is collaboration. Our library service could help increase laboratory safety, but we need the life sciences community to embrace this effort.

Following the launch of the Chemical Safety Library Service in March 2017, requests for access have been overwhelming. The positive response shows just how much the industry is looking for such a resource. But looking is not enough! Ultimately, the more data the Chemical Safety Library contains, the more useful it becomes to the entire industry. We need companies to move beyond their reticence to share and to add data on hazardous chemical reactions. The process only takes a few minutes. Safety is everyone's concern and now every researcher can embrace the responsibility and do something constructive about it.

For more information, visit www.pistoiaalliance.org/projects/chemical-safety-library/

Calling for ANDA Action

Faster review and approval processes could lower drug costs. Can we axe approval times for abbreviated new drug applications down to three months?

By Girish Malhotra, CPhI Worldwide Annual Industry Report member, and President of EPCOT International, USA.

Currently, it takes multiple review cycles – and up to 10 months – for the FDA to approve an Abbreviated New Drug Application (ANDA). In my view, this is a fundamental flaw with the system and we need to find a way to fix it. We improve every repetitive task to facilitate our daily lives – and in pharma we also constantly improve manufacturing processes – so why not improve the ANDA application filing and approval process?

I keep banging the drum, but not enough of the industry is willing to face the challenge. I am not questioning the authority of the FDA or other government bodies, but I do believe that as an industry we need to consider how we can refine our processes. Yes, this is a challenging task, but until we take on the challenges, progress will never be made. And it will all be worth it if we can make regulatory process improvements that allow us to consequently lower the overall cost of drugs.

I believe that we could potentially reduce ANDA approval times by two thirds – from 10 months to three months. To achieve this reduction, there are two main challenges that we need to overcome as an industry. The first and foremost challenge relates to submission completeness. It takes, on average, 45 days for the FDA reviewer to determine application completeness. Fortunately, the FDA itself also seems to be interested in making some changes. In March 2017, the Pre-ANDA program was proposed by the FDA, with the goal of clarifying regulatory expectations for prospective applicants early in product development, and reducing the number of review cycles to obtain ANDA approval. But perhaps we can push this further. Much like manufacturing processes, applications for every product are going to be different when it comes to content, but the information filing requirements are essentially the same. For example, the use of a template application/standard format that covers 90 percent of the filing requirements could reduce four reviews down to a single review. To avoid confusion and delay, the FDA would have to clearly state what is expected from companies. Workshops designed to train industry staff on the application template and requirements would allow the Pre-ANDA program to be implemented efficiently. I know such processes work from my own personal experiences – we had a similar

"We improve every repetitive task to facilitate our daily lives... why not improve the ANDA application filing and approval process?"

process at the Illinois Environmental Protection Agency in 1972 for various industry segments, with timelines from submission to approval of equipment design and operating permits. Based on our questions, every industry submitted relevant information that facilitated review and approval.

The second challenge stems from the volume of applications – a difficult issue to address. But perhaps applications can be minimized if the FDA considered a more streamlined process. The agency's operational finesse strategy may have to change, but many businesses deal with such changes.

There are additional elements that the FDA would need to consider; for instance, given that brand companies use risk evaluation and mitigation strategies to delay generic entry, the FDA must develop its own strategy to prevent such harassment. And the FDA or US legislature may also need to intervene and assure that necessary samples are available to potential generic companies to complete their studies for approval. Another interesting point I would like to raise is that if the ANDA approval process was lowered to three months, the need for "priority review" would likely disappear entirely.

Finally, the 90-day timeframe can be broken down into three segments. The FDA could complete the initial review within 15 days; companies would then have 30 days to respond to the agency's requirements. The FDA would then have 45 days to review the application and return to the company with a final proposal. Companies that cannot fulfil all obligations after the 15-day FDA review and the 30-day deficiency completion would have to start the process over. The result? Faster review times – and companies would be encouraged to get it right the first time around.

Serial Killer?

Serialization is more than just adding a number to a box – data management will be the key challenge. And the deadline is fast approaching...

By Jean-Marie Aulnette, Vice President, EMEA Sales, at TraceLink, UK.

Serialization deadlines are nigh; the US regulations, part of the Drug Supply Chain Security Act (DSCSA), come into force in November this year – and any company with a commercialized product in this market will need to be compliant, meaning that manufacturers, contract packaging companies, wholesalers and distributors must all be able to exchange information concerning the journey of the drug throughout the supply chain. All stakeholders, including relevant authorities, need to be able to retrieve this information.

Europe has also set a deadline for track and trace of commercialized pharma products via its Falsified Medicines Directive (FMD), which comes into force in 2019. The FMD aims to enable medicines to be tracked across the pharma supply chain, and to help verify authenticity and eliminate counterfeit drugs. Manufacturers will be required to mark each drug product with a serialized code and the data need to be submitted to the European hub.

Serialization – and track and trace – is not just about adding a serial number to a box, it's about managing the data and transactional information associated with the movement of the drug throughout the supply chain, including when it is first stamped, when it is received, when there is a change of ownership between companies, and so on. And that's potentially tens of thousands of times more data than pharma companies are used to managing. The data must be securely stored – but also accessible at all times. For example, if an authority calls to verify the data, a company will have 24 hours to retrieve the information relating to the transaction document that has been exchanged between owners at a certain point in the supply chain. The complexities surrounding data storage and management have led many companies to outsource their IT infrastructure, specifically to implement cloud solutions, as they offer the capacity to manage large volumes of data while facilitating easy access.

"That's potentially tens of thousands of times more data than pharma companies are used to."

Is the pharma industry ready for serialization? A good question – and the answer depends on which companies you ask. Major pharma companies have

been preparing for the impact that serialization will have on their product portfolio and the wider supply chain for many years. Many mid-sized and small companies, however, are lagging behind – and that includes contract manufacturing organizations.

When implementing track and trace, pharma companies need to look at both their internal and external production and, from an internal standpoint, consider how many packaging lines they will need to equip, and how they can manage the volumes of product and data for each individual market. Companies that outsource production, on the other hand, need to undertake a full and careful analysis of external partners to identify how ready they are, and also how they plan to exchange data safely and securely.

The industry is (painfully) aware that the clock is ticking. One of the biggest misconceptions around serialization is the time and effort required – it's enormous. Large companies have been able to create full teams dedicated to serialization, but this isn't possible for many smaller companies. Common issues include problems at the production site level, such as implementing the necessary hadrware, software and cloud capabilities. Most companies also focus on their own production site before realizing they also have to manage their external network or ecosystem. As soon as you have to exchange data with external partners, who are potentially sharing data with multiple companies, you are faced with the big question of the standards that are used to exchange data (and I recommend a standardized approach).

With multiple production lines to equip, there is the potential for bottlenecks – particularly as the resource availability of the market is becoming more limited as everyone rushes to meet the deadlines. Once again: serialization is not a short-term project – you need to act sooner rather than later.

Remember that not all solutions are equal. As serialization involves managing and sharing data among a complex web of supply chain partners, pharmaceutical companies should consider joining a large network that allows them to simplify the process. But bear in mind that looks can be deceiving; anyone can create a website or portal, but infrastructure that is able to manage large volumes of data is the most important aspect. In the world of compliance, nothing beats experience.

JM Johnson Matthey

Inspiring science, enhancing life

CELEBRATING 200 YEARS OF HISTORY

The roots of Macfarlan Smith extend back to the early nineteenth century, when John Fletcher Macfarlan sets up his pharmacy in Edinburgh. This is later acquired by Johnson Matthey in 2001.

Denatonium benzoate (Bitrex®) is identified. It is extremely bitter and is readily detected in the air and in any solution. It is later recognised as the bitterest substance in the Guinness Book of Records (1982)

1815

1817

Percival Norton Johnson establishes business as a gold assayer, this later becomes known as Johnson Matthey.

1854

Macfarlan Smith morphine is used in the first-ever hypodermic injection into a human.

1870

J.F. Macfarlan works with Joseph Lister, the pioneer of aseptic surgery, and produces the first sterile dressings.

1958

1970

Research with Michigan State University begins. This later leads to discovery of the platinum-based anti-cancer drugs cisplatin in 1977 and carboplatin in 1975. Johnson Matthey later commercialises platinum-based anti cancer drugs in 1983.

Johnson Matthey, a global leader in science that provides cleaner air, improved health and more efficient use of natural resources, is celebrating its 200th year in existence. To mark JM's bicentenary, the company is taking a look back at some of its biggest achievements so far within the Pharma industry. JM is well known for being responsible for the first hypodermic injection into a human in 1854, as well as pioneering aseptic surgery and, in 1870, producing the first sterile dressing. JM also played a major role in discovering and developing the platinum-based, anti-cancer drugs, carboplatin in 1975 and cisplatin in 1977, which are today among the world's most successful cancer drug treatments. More recently, the company acquired the Pharmorphix® solid form business, bringing world-leading solid state capabilities to JM. Over the past 200 years JM has established itself as a world leader within the Pharma industry, and will continue to innovate and solve complex chemistries to enhance people's quality of life.

Johnson Matthey expands its API capabilities in the US as the West Deptford plant opens for manufacturing.

1983

1985

Johnson Matthey expands its capabilities into Controlled Substances to gain synergy with existing security infrastructure for Precious Metals.

2001

Development of large-scale chromatography and separations work at Devens, MA facility begins. In 2005 this facility can handle high potency operations.

Johnson Matthey acquires Pharm-Eco Laboratories and Synetix to strengthen its API and catalysts offerings.

2002

Johnson Matthey acquires the former GSK manufacturing site in Annan, Scotland. Considerable investment in this site leads to successful MHRA certification in 2016.

2014

2015

Johnson Matthey acquires Pharmorphix® solid form business from Sigma-Aldrich bringing world-leading solid state capabilities.

2010

Acquisition of X-Zyme means the addition of a biocatalysis platform to JM's catalysts offering.

Asia expansion: commission of the Yantai, China facility and in 2011 the opening of the Shanghai catalyst plant.

PHARMA'S GREAT GREEN *RUSH*

Cannabinoids – naturally found in cannabis – and the human endocannabinoid system are proving to be an intriguing target for drug discovery. But what is the real value of this ancient medicine?

By Stephanie Sutton and James Strachan
Images Courtesy Of CMW Media

"It is beyond my comprehension that any humane person would withhold such a beneficial substance from people in such great need simply because others use it for different purposes."

– Steven Gould, American sci-fi author

Cannabis leads a double life. On one hand, it is a recreational drug, the regular use of which has been linked with lower fertility (1), increased risk of psychotic illness (2), and, for heavy adolescent users, impaired intellectual development (3). On the other hand – looking beyond the smoke and the stoners – it has been used medically for thousands of years. Cannabis is one of the 50 fundamental herbs in traditional Chinese medicine, and its use has been traced to ancient Egypt, India, and Greece, among others.

Countries began banning the sale and use of cannabis in the 1900s because of its psychotropic properties but, in recent years, there have been calls to ease regulations as scientific studies delve deeper into the plant and its many chemical compounds – cannabinoids in particular. A big breakthrough in the field was the discovery of the human endocannabinoid system in the 1990s. The endocannabinoid system – in essence, the body's own cannabinoid system – is believed to be associated with a number of physiological processes, affecting memory, mood, sleep and stress (4). Cannabinoids act directly on the endocannabinoid system, which instantly makes cannabis very intriguing from a drug discovery point of view, especially now that we have a greater understanding of which cannabinoids are responsible for the euphoric high associated with recreational cannabis use and which cannabinoids may offer other health benefits. Some countries have now legalized cannabis for limited medical uses, and academics and commercial companies alike are rushing to uncover the plant's true therapeutic potential – and value.

Cannabis and cannabinoids (both synthetic and botanical) are being investigated for a variety of indications including pain, Alzheimer's, cancer, glaucoma, epileptic seizures, diabetes, and mental health, and a small number of medicines, mainly based on synthetic cannabinoids, have already reached the market.

We speak to experts in cannabinoid drug development to take stock of this rapidly growing field.

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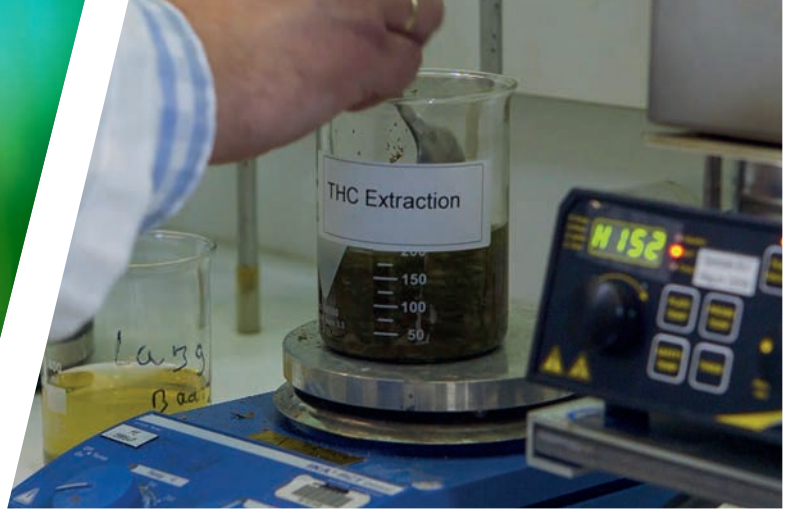

A CAREER IN CANNABINOIDS

The complexities of the cannabis plant have made it a fascinating research target for years. And Roger Pertwee is one of the most prolific researchers in the field.

Roger Pertwee, Emeritus Professor at the University of Aberdeen, UK, and Director of Pharmacology at GW Pharmaceuticals, has spent 50 years studying the pharmacology of cannabinoids and made major contributions to the field, including the co-discovery of the first endocannabinoid – anandamide – and thus the endocannabinoid system. He is a co-founder of the International Cannabinoid Research Society and has received numerous awards for his work, including the 2011 Wellcome Gold Medal by the British Pharmacological Society.

How did you first become interested in pharmacology?

I was reading for a degree in biochemistry at the University of Oxford where the Head of Department was the famous scientist, Hans Krebs. During that time, I joined the OU Officer's Training Corps (Royal Engineers), which gave me the opportunity to spend a couple of weeks at Marchwood, near Southampton, to undergo training as an army shallow water diver. As a result, I became aware of the phenomenon of inert gas narcosis ("raptures of the deep") – early signs of general anesthesia that can be induced by compressed air when inhaled by a diver at certain depths. I was intrigued by this then little-investigated phenomenon to the extent that once I had obtained my degree (in the summer of 1965), I approached the Royal Naval Physiological Laboratory at Portsmouth for advice on how I might begin research into inert gas narcosis. I was directed back to Oxford – to Professor Bill Paton, Head of the Department of Pharmacology and a world-renowned expert on the pharmacology of anesthetics. He took me on as a student in October 1965.

And how did you come to focus on cannabinoids?

Around the time I was carrying out my DPhil research, cannabis had just emerged in the UK as a significant recreational drug, prompting the need for research to investigate its then largely unexplored pharmacology. Since the constituents of cannabis were known to be very lipid-soluble, Paton was interested in investigating the possibility that one or more of these constituents might affect brain function (for example, to produce a "high") by acting like a general anesthetic (at a sub-anesthetic dose) potentially by affecting the "fluidity" of cell membranes. Because

A sample of cannabinoid-related discoveries made by Roger Pertwee and colleagues

- The development of new bioassays for exploring the pharmacology of cannabinoids.
- The co-discovery of anandamide and the endocannabinoid system – an important potential therapeutic target.
- The discovery of an allosteric site on the cannabinoid CB1 receptor.
- The discovery of some of the pharmacological actions of certain chemicals (phytocannabinoids) present in cannabis, and hence of new potential therapeutic uses for some of these compounds – for example, the elucidation of the mechanisms of action and unique therapeutic potential of delta-9-tetrahydrocannabivarin (THCV) and of cannabidiolic acid (CBDA).
- Contributing to the eventual development of a cannabis-based medicine (Sativex) for multiple sclerosis (MS) – first, by interacting in the 1990s with MS patients who were self-medicating with cannabis, and with MS scientists and clinicians, and publishing findings generated by these interactions; and, second, by presenting information about cannabinoids by invitation, for example, to the British Medical Association, and to the Science and Technology Committee of the House of Lords, again in the 1990s.
- In collaboration with others, the pharmacological characterization of synthetic cannabinoids now widely used as experimental tools – e.g. AM281, AM630, methanandamide, ACEA and ACPA
- The co-development of a water-soluble synthetic cannabinoid that can activate cannabinoid receptors.

I had been working on the pharmacology of general anesthesia for my DPhil, Paton took me on as a post-doctoral research assistant to work on the pharmacology of cannabis and some of its constituents. I was very lucky to enter what turned out to be a fascinating field of research, at a time when so little was known about cannabinoid pharmacology.

What challenges have you faced in the field?

There is a good system in place in the UK for obtaining a license that allows a scientist to perform valid research with cannabinoids, so there haven't been any regulatory hurdles. One challenge I have faced, however, was the fading interest in cannabinoid pharmacological research in the mid/late 1980s – many felt, at the time, that there was nothing new that needed to be, or could be, learned about cannabis. However, all that changed with the discovery of cannabinoid receptors – and the cloning of the CB1 receptor in 1990 – along with the subsequent discovery, in 1992, that we humans produce cannabinoids (endocannabinoids) in our own bodies that can activate cannabinoid receptors. The first of these endocannabinoids, anandamide, was discovered, partly in my lab, in a project led by Raphael Mechoulam, and generated important new reasons for carrying out cannabinoid research.

One of the questions facing the research community is whole-plant extracts versus individual cannabinoids. What are your thoughts?

The goal – and challenge – is to develop new cannabinoid medicines with optimal benefit-to-risk ratios. This will most likely be achieved using individual synthetic or plant-derived cannabinoids, either by themselves or in combinations of two or more cannabinoids, in optimized ratios.

There is also the question of whether to develop synthetic cannabinoids or botanical cannabinoids as medicines. I believe there is a place for both. Examples of a synthetic cannabinoid medicine could include an inhibitor of endocannabinoid metabolism or a positive allosteric modulator of cannabinoid receptors that augments "autoprotection" resulting, for example, from the activation of cannabinoid receptors by endogenously released endocannabinoids; a structural analogue of a plant cannabinoid that displays greater stability; a peripherally-restricted synthetic cannabinoid that cannot enter the brain to target central cannabinoid receptors, but can still activate or block cannabinoid receptors located outside the brain to produce various effects, including therapeutically beneficial ones; and/or a medicine with a set of pharmacological properties that give it a particularly high benefit-to-risk ratio.

What is needed to help boost cannabinoid research?

More clinical research is needed to establish the accuracy of the vast amount of preclinical evidence predicting new therapeutic areas for cannabinoids. That said, there remains a need for yet more preclinical pharmacological research directed at exploring the pharmacological actions of known cannabinoids more completely, as well as developing new cannabinoids and exploring their pharmacology and therapeutic potential. There is also a need for more extensive research into the central and peripheral roles of the endocannabinoid system.

CANNABIS COMPLEX

The cannabis plant contains hundreds of different compounds – and most are difficult to formulate – but if overcoming the complexities means new medicines for unmet needs, it's worth it.

By George E. Anastassov

The term "medicinal marijuana" is becoming increasingly used by patients and members of the public, but it is also a misconception – medical cannabis has not been registered as a medicine in any country and, to date, only a small number of cannabinoid medicines (mostly based on synthetic cannabinoids) have reached the market. Legality, of course, is one challenge for the field, as are the negative perceptions stemming from the use of cannabis as a recreational drug, but there are also significant scientific hurdles – the cannabis plant is extremely complex, with over 100 cannabinoids and over 700 other compounds, such as flavonoids and terpenes.

Some researchers take the viewpoint that cannabis should be used in its whole form because the mixture of different compounds are what give the plant its intriguing medical properties. However, the scientific community still does not understand what every substance in the plant does, which will make it very difficult to turn the plant into a regulated medical product. The active pharmaceutical ingredient in most medicines is a single molecule that can easily be characterized. If a medicine contains two or more active molecules then development is more difficult because you must investigate the interactions between the molecules – and if you have 700 different compounds then thorough investigation becomes virtually impossible. The consequences of getting it wrong are severe. In 2016, there was a disastrous clinical trial in France involving the testing of a fatty acid amide hydrolase (FAAH) inhibitor, which resulted in a patient death. FAAH inhibitors aren't based on cannabinoids, but FAAH is part of the pathway that cannabinoids target. Such disasters highlight the challenge of synthesizing safe compounds when you do not fully understand the biochemistry and pharmacology involved.

Today, those working to develop cannabinoid-based therapies are mainly focusing on just a handful of cannabinoids, including THC, CBG, and CBD.

Chewing over challenges

I became interested in cannabis around 15 years ago, when a colleague and I were looking for novel classes of painkillers. We were very dissatisfied with what was on the market at the time (and little has changed since then) – yes, we have opioids and non-steroidal anti-inflammatories, and combinations of the two, but these drugs can have severe side effects. Eventually, we became interested in cannabinoids, partly because cannabis has been used for pain relief for thousands of years in many different cultures.

Today, I am the Chairman, Chief Executive Officer and President of AXIM Biotechnologies, which is developing a

Did You Know?

- At least 113 different cannabinoids have been isolated from the cannabis plant – the most abundant cannabinoid is cannabidiol (CBD).
- The main psychoactive component of cannabis is tetrahydrocannabinol (THC), which was first isolated in the 1960s.
- Cannabis today is 57-67 percent more potent than it was in the 1970s (EL Sevigny, "Is today's marijuana more potent simply because it's fresher?" Drug Test Anl., 5, 62-67 [2013]).
- The global market for medical cannabis is predicted to reach $50 billion by 2025.
- Israel is considered the global leader in cannabis research.
- Historical figures who some have argued were users of cannabis include William Shakespeare, Queen Victoria and James Monroe. Letters also show that George Washington grew cannabis.
- In 1619, in the Jamestown settlement of the Colony of Virginia, legislation was passed that made it illegal not to grow hemp.
- Cannabis and beer are botanically related – hops also belong to the Cannabinaceae family.
- Proponents of cannabis claim there are no documented deaths due to cannabis and that it is almost impossible to take a lethal overdose; however, cannabis users are more likely to be involved in road traffic accidents (RE Mann et al., "Cannabis use and self-reported collisions in a representative sample of adult drivers," J Safety Res., 38, 669-674 [2007]).

variety of pharmaceuticals, nutraceuticals and cosmetic products. One of our main focuses is on cannabinoids, and we are working on nine different formulations for fourteen different indications, including pain, eczema, psoriasis, vitiligo, dry eye, and irritable bowel syndrome – results from our Phase II clinical trial for irritable bowel syndrome (being conducted in the Netherlands) are expected very soon.

When it comes to formulation and drug delivery, cannabinoids tend to be very hydrophobic and challenging to work with, but some can be more difficult than others; THC, for example, is extremely volatile and oxidizes at room temperature. Much industry attention has focused on inhalation as a delivery method, but we wanted to investigate alternative approaches and have seen success with a more unconventional drug delivery format: chewing gum. Chewing gum presents challenges in terms of formulation and manufacture, but it also has a number of inherent qualities. For instance, the act of chewing itself is thought to potentially offer neuroprotective properties. If you look at peer-reviewed literature, you'll find a variety of articles suggesting that chewing can improve cerebral circulation, boost memory, and reduce stress. Importantly, the use of chewing gum as a drug delivery vehicle bypasses the gastrointestinal system. Some cannabinoids can be transformed into toxic metabolites when they reach the gut or liver. Inhalation, of course, can bypass this issue, but so too can chewing gum, where the active chemical enters circulation via the trans-oromucosal system.

As well as developing our own innovative medicines using chewing gum and other formulation approaches, we are also investigating how we can enhance older medicines. The first cannabinoid-based medicine approved by the FDA was Marinol (manufactured by AbbVie) in 1985. Marinol contains a synthetic form of THC (dronabinol) and is approved for loss of appetite and nausea. The drug is administered via a gel capsule, but can cause a number of side effects due to first-pass metabolism in the liver, where 90 percent of the active is metabolized. We are currently developing a bioequivalent of Manitol in chewing gum form – and so far we've shown a significant increase in bioavailability (over 70 percent).

A new leaf

I have recently returned from the Cann10 medical cannabis conference, which was held 4-6 June in Tel Aviv, Israel. There were more than 800 participants from all over the world, including representatives from big pharma and the FDA. It's clear that cannabinoids have captured the interest of the industry and although there are still significant challenges hindering research (particularly in the US where cannabis is classed as a Schedule 1 substance), attitudes are slowly changing. In January 2017, the United States National Academy of Sciences released a substantial report – over 400 pages long – that reviews the scientific research conducted around cannabis and cannabis-derived products since 1999. The report includes information on indications where there is clinical evidence for eliciting a therapeutic effect with cannabis. And there are certainly many – perhaps the most exciting prospect is that cannabinoid research may lead to new medicines for diseases that currently have no effective treatment – brain cancer, stroke, myocardial infection, and epilepsy to name just a few.

George E. Anastassov is Chairman, Chief Executive Officer and President of AXIM Biotechnologies, New York, USA.

SMASHING THE STIGMA WITH SCIENCE

Cannabis can be a turn off for investors, but Neil Mahapatra and his investment firm are showing the world that there's nothing to fear – and much to potentially gain – through a collaboration with Oxford University.

Neil Mahapatra was interviewed by Stephanie Sutton

Why cannabis?

Actually, it started with biology and business. Both of my parents were doctors and I read biology at the University of Oxford. After graduation, I started work at Morgan Stanley, then went to the US to study for an MBA at Harvard Business School. After that, I worked directly for Lord Rothschild – managing the Rothschild family's and RIT Capital Partners' investments. Most recently, I set up Kingsley Capital Partners with some friends, which is a private equity and venture capital firm headquartered in London.

Shortly after we set up Kingsley, my mother – who had never touched a cigarette in her life – was diagnosed with stage-four lung cancer, and 18 months later she sadly passed away. At the time, I was seeking anything – a novel piece of research or any left-of-field treatment – that could potentially help. It was in this context that I came across cannabinoid medicines and research suggesting they might be able to treat cancer. I read a number of personal stories of people who had seen their cancer growth slow or disappear after taking cannabis, but they were just anecdotes – right now, nobody truly understands the mechanism by which cannabis may act on tumor cells or other indications. But this is largely because not enough research has been done. In the US, President Nixon placed cannabis in the "Schedule I" category in 1972 – limiting the amount of research that could be done. At the time, scientists were mining many natural products for potential pharmaceuticals, but cannabis was left out.

This led me to think about what I could do to make a difference. I went back to my own plant biology professor at Oxford, whom I hadn't seen in several years, and told him about my investment firm and that we were considering entering the legal cannabis space in the US, and conducting research in the UK. He said he was interested and introduced me to the wider business development team within Oxford's medical sciences division. This kicked off one and a half years of discussions with the university, culminating in the announcement of a research program in March 2017.

What details can you share about the program?

We have established a portfolio company called Oxford Cannabinoid Technologies (OCT). We will be initially investing £10 million and the goal is to to identify and deliver great new therapies for sufferers of acute and chronic conditions around the world by finding out how cannabinoids work. OCT will be working in close collaboration with Oxford University, and will be involved in the implementation and monitoring of the research projects.

The real benefit will only emerge in the next three to four years. In the meantime, we'll be screening a variety of cannabinoids, in different combinations, against a variety of indications. There may be some promise in using cannabinoids as cheaper alternatives to opioids – which would have huge benefits given the opioid crisis in the US and elsewhere.

We will be looking at both synthetic and natural cannabinoids. Personally, I am very interested in naturally occurring cannabinoids. Extracting these from the plants is challenging, but mainly because resources have not yet been placed into optimizing isolation and extraction technologies.

What were the challenges in getting the project up and running?

Regulation has been something of a challenge. In the UK you have to get a series of licenses to do research with cannabis or cannabinoids – which takes time. We also had to get a license to export cannabis to our extraction partner on the continent. That aside, it hasn't been too difficult – especially when you compare the situation with what US-based firms have to deal with. You can't even transport cannabis or cannabinoids across state lines in the US because of the federal illegality.

I expected to face challenges relating to the stigma of cannabis, and I expect we will in the future; however, the vast majority of people we have spoken with up until now have been very supportive of the medical potential. You might think that an esteemed university like Oxford, with their centuries of history, would be concerned about damaging their reputation by working with cannabis: not so! Oxford are brilliant, supportive partners and there are some deeply clever people working on this program. What excites me is that we have all these experts in different fields now turning their attention to cannabinoid medicines.

What is needed to advance the cannabinoid space?

I do think the US should consider legalization changes to cannabis at a federal level, which would make the US a far more attractive destination for international research – and US companies would become more attractive potential partners; there are many companies I would love to work with in the US, but can't because of the regulatory barriers. More generally, I think we need to see even more experienced and professional people moving into the space: the clinical potential is clearly there, but the stigma surrounding cannabis still puts people off. It's important to emphasize that OCT is not in the business of "peddling weed" – we are trying to create drugs that will help millions of people worldwide.

A VIEW FROM THE BIOSYNTHETIC BRIDGE

Regulations in the US make cannabis research highly challenging. Could biosynthetic approaches to cannabinoid production prompt regulators to rethink?

By Jeff Korentur

From a US perspective, cannabinoid-based drug development and research has been particularly difficult because of the designation of the plant. Cannabis, including its cannabinoids, are classified as "Schedule I" drugs, which means they are defined as having "a high potential for abuse," "no currently accepted medical use in treatment in the United States," and lacking "accepted safety for use [...] under medical supervision." Researchers, therefore, need to jump through a number of regulatory hoops to carry out cannabinoid research. It's interesting to contrast the US situation with what goes on in other countries, specifically in Israel, Canada and the UK, which is where most of the breakthroughs are taking place.

In the US, a few states have reclassified and legalized cannabis. For example, Colorado, legalized the recreational use of cannabis in 2012 for individuals over the age of 21. A number of Colorado residents suffering from certain medical conditions can also access cannabis from dispensaries that offer a range of cannabis strains with different qualities. In states where cannabis is legal, it is easier to conduct research, but there are limits. When Teewinot Life Sciences first started, we decided to focus on the biosynthetic production of pharma-grade cannabinoids but it was clear that we would quickly exceed what was legal in Colorado and elsewhere in the US. Today, we are headquartered in Tampa, Florida (which implemented the Florida Medical Marijuana Legalization Initiative in 2016). We conduct our internal research and development in Canada under license from Health Canada, and all our existing and planned intellectual property are housed by our subsidiary in Ireland. In fact, a number of US companies have uprooted and moved overseas to facilitate their cannabinoid research efforts.

Genesis through biosynthesis

To create biosynthetic cannabinoids, we use a production environment that replicates the internal cellular function of the cannabis plant. We can currently produce 18 different cannabinoids, which are identical to those produced by the plant. This is really important because many cannabinoids have multiple chiral centers and when chemically synthesizing cannabinoids it is difficult to avoid stereoisomers, which can have very different effects to their chemical cousins. Our processes use the same mechanism as the plant, so they end up being the same as the compounds produced by the plant. Our approach can include a mixture of organic chemistry, synthetic biology and biocatalysis. The synthetic part refers to changing the structure of an organism, such as modifying a single-celled microbe, to encode performance of a new function required for the overall process. Biocatalysis involves using enzymes to react with a starting material to produce the desired end product. Essentially, we have engineered microorganisms to produce specific synthases found in the cannabis plant. We react these synthases with the same starting material the plant uses, which – depending on the conditions set up within the bioreactor – yields different cannabinoids.

Synthetic biology and biocatalysis are not new to the pharma industry – and are already used extensively for producing medicines. One of the benefits of our process is that it can be used to enhance a naturally occurring molecule. For example, we have developed a pro-drug of CBD that has a half-life of more than 12 hours. Standard CBD has a half-life of around 70 minutes, which means that patients may have to dose many times a day to maintain a particular blood plasma level, whereas boosting the half-life would allow for just a twice daily dose.

Compared with the botanical approach to cannabinoids, the advantages of synthesis are speed and diversity. Botanical extractions usually take between three to four months, whereas chemical synthesis takes around two months to create a limited number of

specific end products. Our process takes between two and seven days, which demonstrates the speed that a biosynthetic approach can bring to cannabinoid production. In addition, a biosynthetic approach removes the need to test for the various contaminants and impurities that may exist within a botanically grown plant. Plants, after all, are living things, which makes them prone to variability, although some companies are seeking to mitigate this reality by using plant clones.

High times

Fantastic research around cannabinoids is being conducted worldwide on a variety of indications, including pain, cancer, metabolic disease, psychiatric disease and much more. It seems clear that there is huge potential for cannabinoids for many unmet medical needs. We still need more research and more methods to investigate the remaining cannabinoids – at the moment, THC and CBD are receiving the most attention, but given that that are over a hundred other cannabinoids, we are only scratching the surface of what could potentially be achieved. Many cannabinoids have no known chemical synthesis route and occur only fractionally in plants, making them commercially unviable to extract. A researcher may hypothesize that a certain cannabinoid will benefit a certain patient population, but unless they can get their hands on the cannabinoid, they will never find out.

For the future, my hope is that our population will recognize there is more to cannabis than getting high. I can, of course, appreciate regulators wanting to limit exposure of psychotropic drugs to the general population, but only a few cannabinoids are psychotropic, which means that a blanket ban does a tremendous disservice to the wider patient population that could be well served by the remaining non-psychotropic compounds. We are currently making the case to a variety of regulatory bodies about rethinking the categorization and scheduling of these non-psychotropic molecules to accelerate the development of new medicines.

Jeff Korentur is CEO of Teewinot Life Sciences.

You can find more content about cannabinoids in the online edition of our June issue available at www.themedicinemaker.com If you'd like to delve even further into the science of cannabis then check out The Cannabis Scientist, at: http://bit.ly/2n9cNkj

A New Dawn for Real Time Characterization?

Advanced tools such as surface plasmon resonance offer scientists a deeper understanding of their biotherapeutics – and unlock the potential for better products for patients.

By Robert Karlsson

In my last article (1), I discussed the benefits of surface plasmon resonance (SPR). As a quick recap, SPR has been around for over 25 years and, in particular, has become a popular method for characterizing biotherapeutics and biosimilars. SPR is label-free, allows for real-time analysis and can characterize binding in terms of kinetics and affinity. In this article, I will explain in more detail some specific examples of how SPR can be used. Biopharmaceuticals are far more complex than defined chemical drugs, so analytical tools that provide in-depth understanding of how upstream and downstream processes can affect the critical quality attributes (CQAs) of a product are crucial for developing an effective bioprocess control strategy.

In the early stages of biopharma development, the focus is often on kinetic analysis, but in later phases, where the manufacturing process is in place, analysis can be simplified. Here, it is important to demonstrate that the drug substance and drug product maintain binding properties, and to determine drug potency to ensure correct dosage. For this purpose, kinetic analysis can be replaced with dose response curves. By comparison with a reference batch, the relative potency can be estimated from median effective concentration values (EC50) or by parallel line analysis (PLA). The output from EC50 analysis or PLA is a concentration. However, EC50 values can also shift because of changes in binding kinetics. To establish more conclusive dose comparisons, GE Healthcare has developed Biacore software that enables direct comparison with established kinetic profiles in a way that avoids kinetic modeling and determination of rate constants. By combining the information obtained from dose response curves and sensorgram comparison, more stringent batch-to-batch comparisons can be obtained than when only using dose response curves. Data for dose response curves and sensorgram comparison can readily be obtained in a single experiment.

To cover all CQAs, an array of potency assays may be required – an aspect recently discussed by researchers from Roche, who developed Biacore assays for their bispecific CrossMab (2). The assay is based on a bridging format that enables you to look at binding of the antibody to two different antigen specificities in a single sensorgram. The final readout, reported as a single response, represents the relative amount of CrossMab molecules that simultaneously bind both antigens.

Though the Biacore assay format is flexible, pitfalls can arise when applying a bridging assay (for example, a change of antigen activity upon immobilization), so the same team developed an alternative SPR-based assay that allowed individual assessment of both targets in solution (3). Comparison of data from the two assays showed that simultaneous binding can be calculated based on both individual readouts and revealed a good correlation. Hence, the SPR-based assay principles enabled "full" functional analysis of a bispecific CrossMab in only one assay.

SPR is also commonly used for biosimilar development to compare the biosimilar with the approved reference product. Indeed, SPR is even mentioned specifically in FDA biosimilar guidelines. Other techniques, including liquid chromatography-mass spectrometry and capillary electrophoresis, are often used in biosimilar development, but they only provide structural information, whereas SPR can be used for functional studies to characterize and compare target and effector function of the biosimilar to that of the reference product. Functional studies are further used to investigate whether subtle changes in higher order protein structure or glycosylation patterns impact antigen or Fc-Receptor binding.

Our Biacore systems are applied in drug discovery, but also increasingly in early development and production, replacing traditional ELISA-based methods and some cell-based assays. In June 2016, we introduced our next generation of Biacore SPR systems. Biacore 8K is a highly sensitive, eight-needle parallel SPR system to boost operational efficiency throughout drug discovery, development and manufacturing.

Having been involved in the development of Biacore systems for more than 30 years, it's no surprise that I'm passionate about their potential. Users are continuously pushing the boundaries of SPR as they seek to better understand their molecules and to develop better products for patients. We are not standing by idly and I expect the technology to continue to advance in leaps and bounds.

Robert Karlsson is staff scientist in the Purification and Analysis team at GE Healthcare Life Sciences.

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NextGen

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Future trends

The Ups and Downs of Drug Development

Pfizer scientists reveal the story behind the world's first JAK inhibitor for rheumatoid arthritis.

By William Aryitey and Stephanie Sutton

Back in the 1990s, Pfizer began investigating how Janus kinases (JAKs) were linked to inflammatory responses – and discovered a promising compound during high-throughput screening. It was rough and not optimized, but scientists saw the potential for a JAK inhibitor. Fast-forward to the present, and a synthetic analog of the compound is now on the market for rheumatoid arthritis (RA). Tofacitinib, marketed as Xeljanz, was approved by the FDA in November 2012 and by the European Medicines Agency in January 2017.

In the human body, diseases often arise when signaling pathways go awry. The JAK signaling pathway helps regulate a variety of functions, including immune responses and hematopoiesis. Since their discovery, JAKs have attracted much attention as a therapeutic target for chronic inflammatory disease. To date, only a few JAK inhibitors, including tofacitinib, have reached the market: ruxolitnib (Jakavi, marketed by Incyte and Novartis), which was approved by the FDA in 2011 for myelofibrosis and polycythemia vera; and baricitinib (Olumiant; marketed by Eli Lilly and Incyte), which was approved by the EMA in February 2017 for RA, but rejected by the FDA in April 2017 (the agency has requested more trial data around dosing). Pfizer's animal health business, Zoetis, also received approval for a JAK inhibitor for treating allergic dermatitis in dogs in 2013. It's still early days for this class of drug, but there are a number of JAK inhibitors in clinical trials for a variety of diseases, including Crohn's disease, psoriasis and ulcerative colitis.

"When we started working on our JAK program in the 1990s, research in the field was in its early days – as was research with other kinases – but was really starting to blossom," says Mark Flanagan, an Associate Research Fellow at Pfizer, who was involved with the early development of tofacitinib. "We started to look at JAKs as potential modulators of inflammatory response partly because of the work performed at the National Institutes of Health by John O'Shea. In the early 1990s, O'Shea was studying

specific mutations in JAK signaling. During an immunology conference, he struck up a conversation with Paul Changelian, an Immunology Biologist at Pfizer, studying suppression of the immune system. Their discussion and scientific curiosity eventually led to a collaborative effort between Pfizer and the NIH."

O'Shea's research gave the team at Pfizer greater confidence and quelled fear surrounding a burning question: would modulating the activity of JAK be sufficient to elicit a therapeutic effect?

A challenging target

In the high-throughput screen that followed, more than 400,000 compounds were assayed against the catalytic domain of JAK. One hit seemed particularly promising, inhibiting both enzyme activity and cellular immune responses. But despite promising early research, there were still questions – both inside and outside of Pfizer – about whether a JAK inhibitor could ever reach the market.

Eileen Elliott (today Pfizer Kendall Square Site Director) recalls the excitement and trepidation of those early days, noting how novel the work was back in the 1990s. "At the time, few kinases had been taken forward as therapeutic modalities – except in oncology. We were interested to see how we could modulate the immune system to dampen it enough to have a therapeutic benefit, but without overly suppressing the immune system, which could cause further issues for a patient," she says. "We were learning constantly from new research in genetics and we applied a number of new technologies, such as structural modeling, which we used to understand how our compounds docked with proteins."

RA has been a challenging target for the pharma industry for decades and so early therapeutics simply focused on pain relief. Says Flanagan, "Finding new drugs for any disease is hard. But when it comes to RA, the root cause is very complex. The industry has been accumulating knowledge around RA for many years to figure out which signaling pathways are the best ones to inhibit."

Today – thanks to improved research around the disease – drugs aim to modify the disease process or inhibit the out-of-control immune response to help prevent joint damage and disability. Most new launches for RA tend to be biologics, which need to be administered intravenously or subcutaneously. But Pfizer was always interested in a small-molecule approach. "We knew there was

How Does it Feel?

How does it feel to help discover a drug that eventually makes it way to the market? With drug discovery and development often taking over a decade, it's hard for researchers in the early stages to know which drugs will or won't make it to market. Even the most promising drugs sometimes fall by the wayside because of unforeseen challenges in development. So when a drug does it make it, it is hugely rewarding for those involved.

"Those of us in drug discovery like to think we wake up every morning and say 'We're going to make a drug today', but really we are driven by the science. We love what we do and I think we all joined this industry because we'd like to one day be associated with something that does make it all the way to patients," says Flanagan.

"It's been a long journey for tofacitinib," Elliott adds. "The work is very fulfilling, but incredibly challenging. I've spent countless late nights and weekends in the lab. I've stood watching machines, waiting for results to emerge. (We have spreadsheets and algorithms to help make sense of the data that comes from our equipment, but we ran the experiments so many times that I could look at the data rolling off the machine and know if it did or didn't work...) So I was really excited when it launched in the US in 2012, and I am filled with pride whenever I see an advert for the product on television – I recorded the first advertisement because I wasn't at home! And it's great to see tofacitinib launching in other countries too. Personally, I really look forward to hearing patient stories about how a drug has improved their lives. The industry has been researching RA for many years and although treatments are available, not all of them work for everyone. When I hear patient stories, it reminds me of why I joined the industry."

a lot of industry activity around biologics, but we felt that an oral therapy would be best – and we had a lot of expertise in this area," says Elliott.

A challenging development process

Back in the early 1990s, many kinases were still being discovered so it was very much unknown territory. "We didn't know how many kinases there were, but we knew there were a lot of them and that selectivity would be a significant hurdle," recalls Flanagan. "In fact, there was quite a bit of skepticism, not only within Pfizer, but externally, concerning whether it would be possible to make a selective enough kinase inhibitor to work, especially in a chronic disease like RA. But we were given the green light to try." Sometimes ignorance is bliss – would the size of the human kinome – over 500 kinases – have been enough to turn the green light to red?

Flanagan and fellow Pfizer researchers began the unenviable task of working through the many design cycles needed – monitoring potency and selectivity, and tweaking the drug structure as they went. Eventually – over 1000 synthetic analogs of the original lead later – they identified tofacitinib, which ticked all the right boxes – including selectivity. Flanagan admits that the long and winding struggle to balance all the necessary properties cast doubt over tofacitinib's future more than once. But perseverance pays. "One 'eureka' moment came at a time when we felt we might not be able to progress any further. While making new sets of analogs and testing them in our assays, we found that if we put one methyl group on the molecule at a specific location, it resulted in a ten-fold improvement in potency, as well as a large improvement in terms of the kinase selectivity of the compounds."

More challenges came during scale up. The specialized synthetic chemistry used to build the molecule was easy to perform in the lab, but significantly more difficult at commercial scale. "One example was putting a side chain on a molecule called a cyanoacetamide," says Flanagan. "It was really tricky to pull off, but the process development team came up with some brilliant chemistry to overcome the problem. The whole development of tofacitinib was about collaboration."

"Pfizer's story illustrates just how lengthy (and expensive) drug development can be."

Celebrating milestones

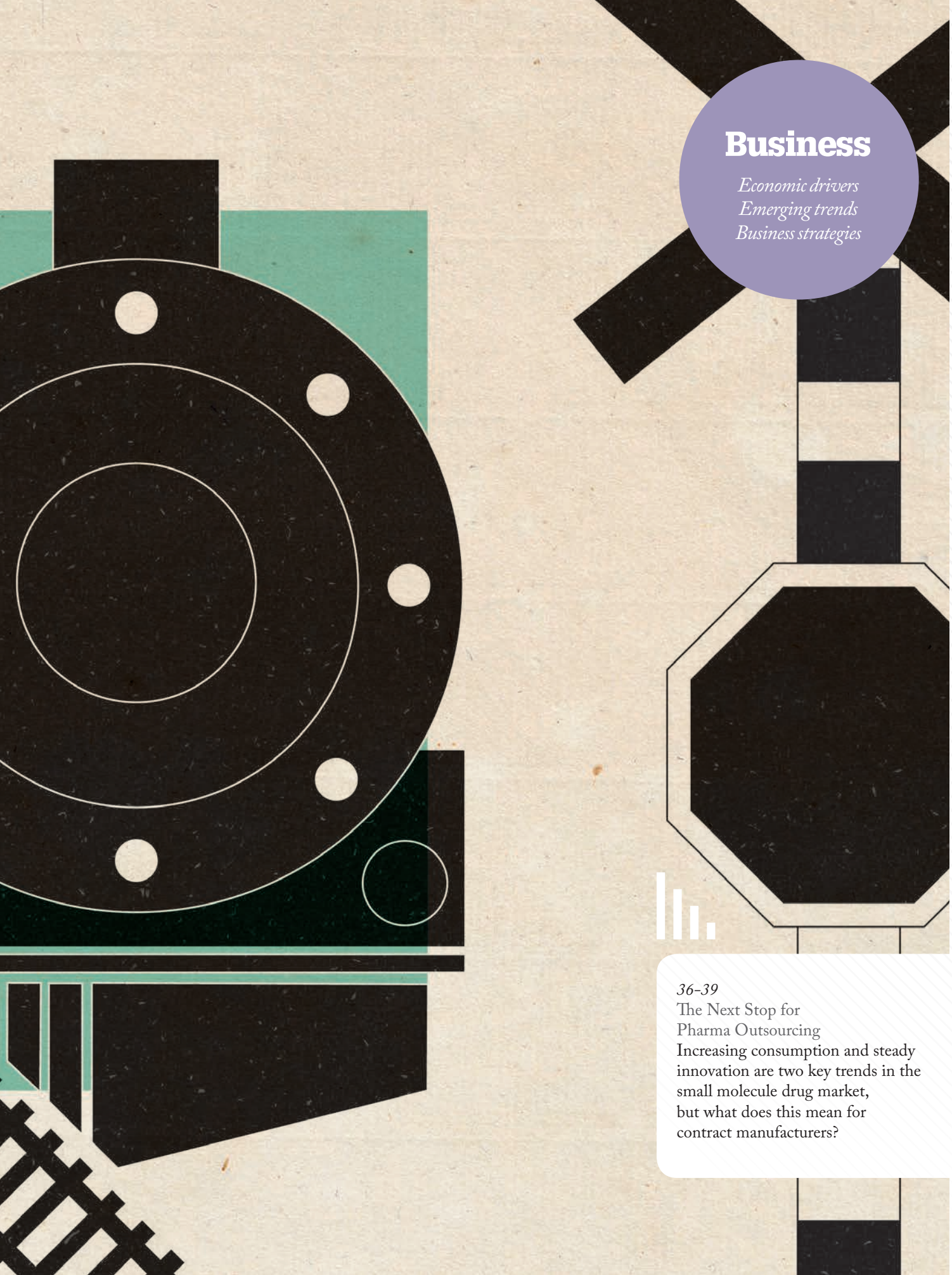
Pfizer's story illustrates just how lengthy (and expensive) drug development can be. It took almost 20 years of discovery, development and clinical testing for tofacitinib to be approved by the FDA – and even longer to gain EMA approval. But Flanagan notes, "You need to remember that JAK inhibitors were really new at the time. We were the first company to work with this set of enzymes; it takes a little bit longer when you have to perform the more basic exploratory research. When we started work on our JAK programs, there were no crystal structures of any of the JAK enzymes. All of the work we did was empirical."

Elliott adds that, given the challenging journey, it was important to set milestones and to celebrate achievements. "When we found the molecule that had an effect in our in vitro assays, we celebrated. Achieving potency was another huge milestone – and celebration. And then we had to build in other functions, such as oral bioavailability and a good safety profile, and every time we checked a box, we saw it as an achievement."

Over the intervening years, Elliott's role at Pfizer has changed considerable. But even though she moved away from early discovery and tofacitinib, Elliott stayed up to date with progress. "Pfizer's team is large but very inclusive and I always received updates from studies and exciting results. The drug discovery process is long and arduous, and the number of failures far outweigh the number of successes. Some people in this industry go their entire careers without ever having a successful molecule make it to market, so I always followed the story with a great deal of pride."

Since the 1990s, drug discovery and development processes and technologies have advanced significantly. Today, Flanagan notes that there is greater use of computational chemistry early on in programs, which enables molecules to be designed and assessed in silico – "It tends to speed up drug development programs and we get to decision points more quickly and make better compounds," he says. "But sometimes there's no substitute for getting in the lab, making the molecule, and seeing how it works!"

Says Elliott, "It's a very exciting time to be working in the pharma industry. There have been tremendous advances in drug discovery technologies, which result in better medicines for patients. A number of previously life-threatening or debilitating diseases have been wrestled into reasonably managed chronic diseases. And we're also moving into the curative space with some incredible activity around cell therapies. I actually believe that the industry is on the cusp of new types of therapies for many different diseases. Such breakthroughs are thrilling to see no matter where they originate from in the industry."



Business

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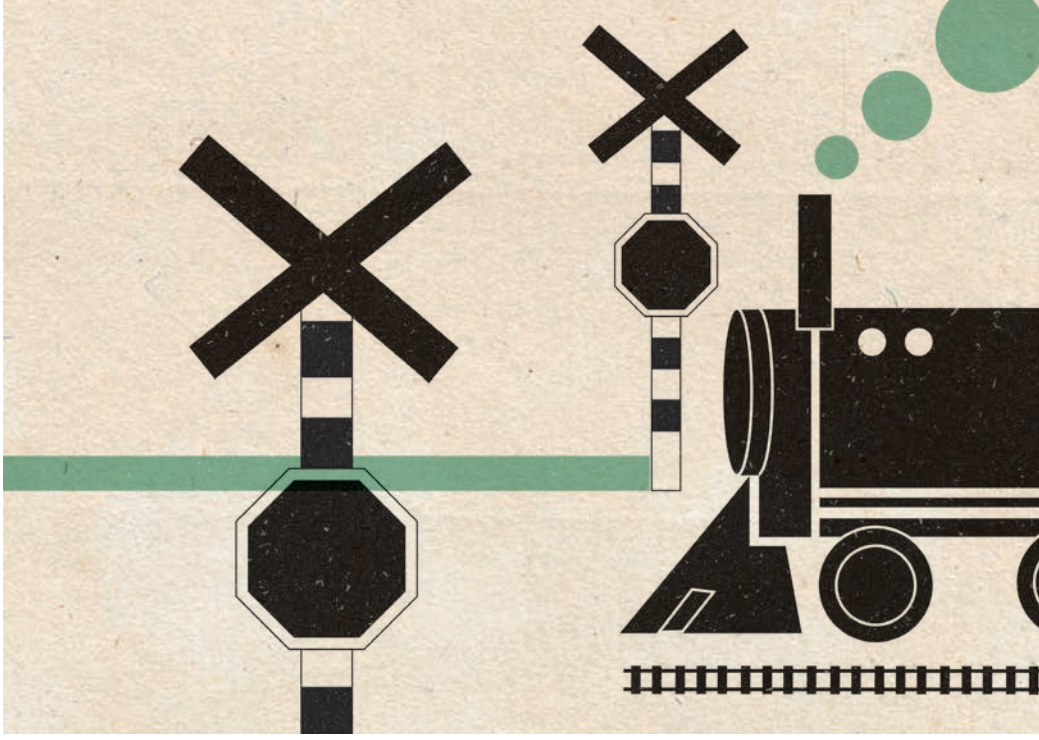


The Next Stop for Pharma Outsourcing

Increasing consumption and steady innovation will be key trends in the small molecule drug market. But what does this mean in terms of contract manufacturing?

By Matthew Moorcroft

In the May issue of The Medicine Maker, I looked at how the field of contract manufacturing has evolved over the past 40 years (1). As a quick recap, my colleagues and I at Cambrex have been studying how contract manufacturing for small molecule drugs has changed since the 1970s (2). Our research showed that there have been four key phases to date: the early years (pre-1975 to 1980), the growth years (1980-1996), the competitive years (1996 to 2010), and the resurgent years (2010 to 2015). Our research was based not only on global API consumption data, the number of new drug approvals and the number of new entrants in the contract manufacturing organization (CMO) space, but also on expert views from leading figures working within the sector.

Reviewing the past is certainly very interesting, but the future is perhaps more important. What can we expect to happen in the lead up to 2020? Extrapolating from the research, I believe three key trends will shape the future of the CMO industry:

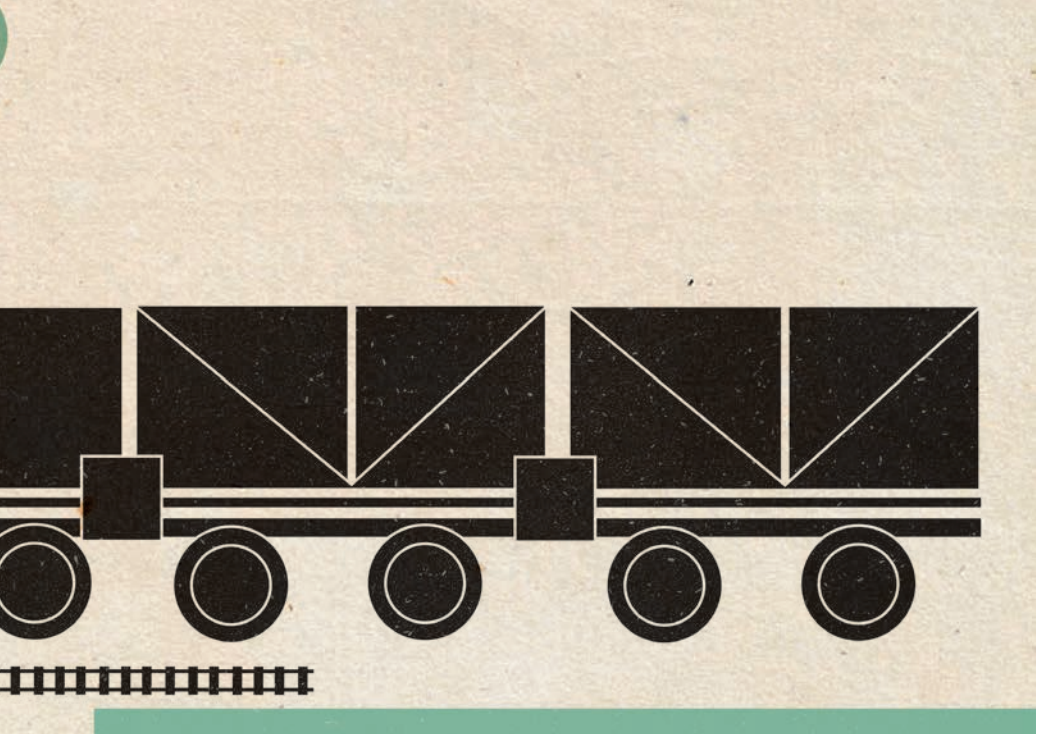
- Increasing consumption. It is well accepted in the industry that there is a tendency towards the manufacture of smaller volumes of API, but this will be offset by more people taking more medicines in the future. Growth in generics will also continue to drive consumption higher.
- Steady innovation. Despite the benefits of biopharmaceuticals, small molecules will remain the backbone of the pharmaceutical industry. Competing modalities will continue to surface, but approvals for small molecule drugs are expected to remain steady at 25-35 NCEs per year.
- Dynamic CMO space. As pharma companies continue to increase their small molecule outsourcing, the way CMOs do business will continue to evolve. There will be a further shake-out of under-performing CMOs, as well as sustained M&A activity as CMOs try to gain market share, move into early- and late-stage development, and gain access to new technologies.

"CMOs have to get used to working with both 'juggernauts' and 'gymnasts'."

Rickety tracks

All of the above trends appear to point towards a positive future for the CMO sector – and for pharma innovators who will be able to reap the benefits of strong contract manufacturing services. But the experts we spoke to warn that there could be risks for CMOs further along the tracks, as many pharma manufacturers may decide to move their outsourced operations back in house. Here are some intriguing comments from the experts we spoke to:

- "The first risk is that whilst western CMOs are enjoying a period of re-shoring and pharmaceutical companies have no obvious plans to explore eastern CMOs just yet, the discussion of building captive capacity, again, could become a real threat. As Cambrex research has shown, the typical volume requirement for a blockbuster product has migrated from the 100 metric ton (mt) range to the 1-10s range. Such a contemporary volume demand makes the prospect of building 'mid-size' internal capacity no longer a ridiculous or arcane idea."
- "Another risk is that the lack of innovation undertaken in CMOs, largely at the request of large pharmaceutical customers who



come with a well-developed tech package, has ultimately starved the CMO industry of some core differentiators. If pharmaceutical companies, with their new, ample in-house manufacturing, no longer look to CMOs solely as capacity-for-hire then there needs to be a compelling argument to continue to outsource."

- "We have come full circle back to 1975, where a CMO existed only to offer a specialism based on a type of chemistry that the customer could not/would not want to do. By lacking that unique selling point, in this environment it will make the outsourcing argument in the customer's decision-making process less and less compelling."

The CMO space is also changing; cost is no longer the historically critical factor that it once was. Instead, CMOs will need to decide if they are in the capacity game or the technology game – both of which have their merits. Capacity, for example, is often needed by pharma companies, but also has downsides. "If you are in the capacity game, the risk is that big pharma will use you as a 'cheap date', where they will use you when they need capacity – but drop you quickly as soon as they don't," said one industry expert. "To mitigate this, CMOs have started to ask for commitments up front. This is not seen as such a difficult thing for big pharma to honor, given that the cost of having idle capacity at the CMO (but for which you are paying a fee) is a lot less than the potential costs of not being able to supply the in-market demand."

Being in the technology game can require significant investment and expertise, but can also help a CMO to differentiate itself, not only from its competitors, but also from big pharma internal manufacturing operations. "A CMO must continually strive to be working on the next technology, even in times when the order book is full and capacity utilization is high," explained one expert. "The best CMOs are those that have adapted and moved with the industry – whether by adopting a specialty technology or moving into the next level of innovation, such as monoclonal antibodies, gene therapy, oligonucleotides, and so on."

"Be an expert. There are a few CMOs who do all molecule/technology types, and then those who specialize in a single technology," added another contact in the industry.

Relationship issues and data

For CMOs that want to be well prepared for the future market, relationships and data will be key. A CMO's relationship with its customers has been important since the early days of contract manufacturing – and this will continue to be important in the future, but will become more challenging. A CMO needs to be of sufficient size to be able to offer a wide enough range of services, technologies and manufacturing capacities to satisfy customer demand, but not be so big that bureaucracy, inertia and inflexibility make it difficult to work with. Experts said:

- "Offering transparency and an open approach to the partnership builds trust. Also thinking about the whole journey rather than a particular half-year or quarterly period is important. For example, it is easy for a CMO to force a customer to adhere to a particular contract – but this is myopic if the relationship is based on a long-term approach – and an example of such is occurring in the biologics CMO industry. Customers have long memories in this industry."
- "CMOs will have to become more flexible in their approach to making deals with customers. Whilst big pharma is traditionally very conservative and operates in the classical fee-for-service, with some shared accountability, other pharmaceutical companies are less rigid and require different business models from their CMOs. As a general rule, across the industry it is a perception that CMOs need to become more flexible and easier to work with – an example of which might be adopting a greater risk/reward profile."
- "CMOs have to get used to working with both 'juggernauts' and 'gymnasts'. Big Pharma applies this juggernaut approach and expects or demands preferential pricing models. Gymnasts (or specialty pharma) adopt a more partnership mentality, based on mutual sustainability and success."

Experts spoken to as part of this research:

- Simon Edwards, VP, Global Sales & Marketing, Cambrex
- Kent Kent, Senior Director, Chemical Manufacturing, Gilead
- Paolo Russolo, President, Cambrex Milan
- Peter Lyford, Commodity Director, GlaxoSmithKline
- Carl Johansson, Global Director, Proprietary Products, Cambrex
- Dix Weaver, Consultant, Weavchem LLC
- Jan Ramakers, Consultant, FCCG
- Rob Miotke, Consultant, Advantage Pharma Solutions LLC
- Jim Miller, President, PharmSource
- Steven Cray, Director, Supplier Relationship Management, Shire

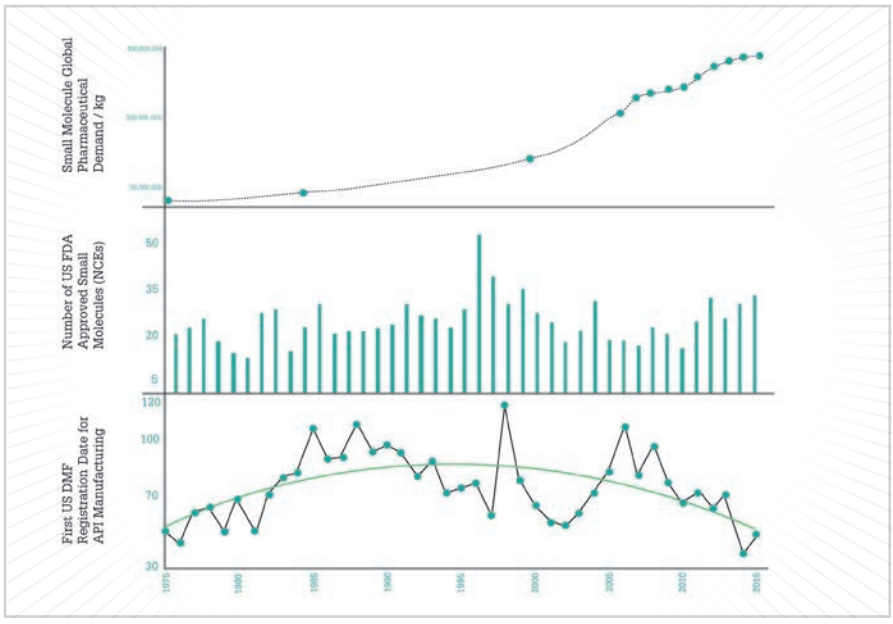


Figure 1. Trends in API consumption, New Chemical Entity approvals, and CMO entrants.

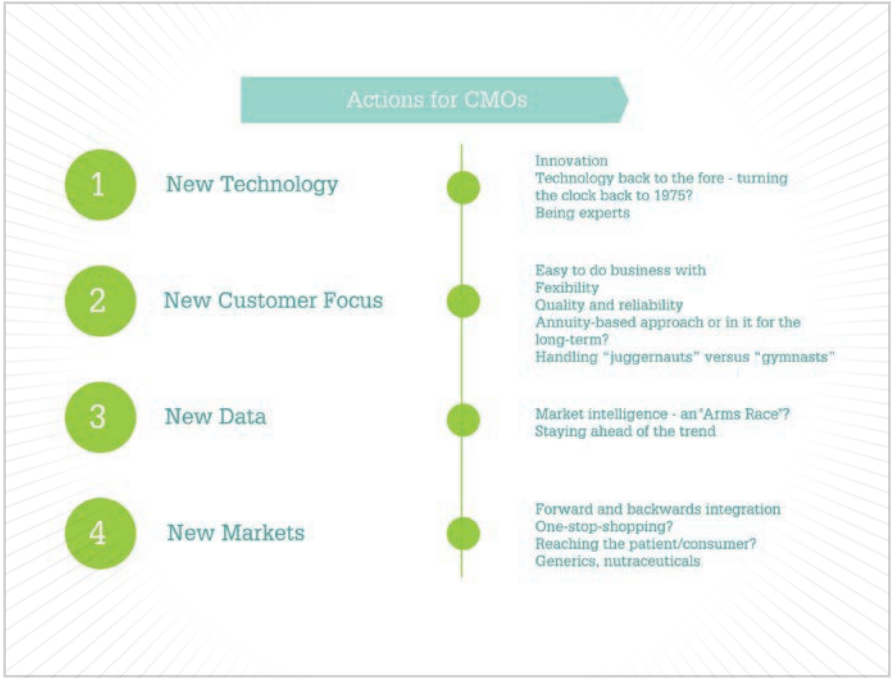


Figure 2. CMO actions to prepare for the coming years.

As for data, right now there is an "arms race" among CMOs to use market data and analysis – and with good reason, as being able to anticipate market trends is an effective way to react to the rapidly changing market. "The pace of change in today's business environment – such as new markets and new technologies – is frantic. Things change so much more quickly nowadays than they did back in the 1980s!" said one expert.

Another added, "It is important to invest in market intelligence to 'take a few bets' on the next blockbuster products that are still at the early stage. Sitting and waiting for the next large-scale Phase III product is not a viable business model, and making a few early stage bets on pipeline molecules is hugely important – using the appropriate data."

Further down the tracks

For CMOs looking to grow in the coming years, the most important strategic decision will be developing an approach to secure new markets. One obvious way to do this is to back-integrate further upstream into the production of intermediates, or to forward-integrate into making drug product – or even both.

"As more and more steps in a chemical synthesis come under the scrutiny of the regulatory authorities, there has been a trend to push back the regulated starting material to earlier in the process," said one expert. "This has led to the need for more GMP manufacturing of intermediates."

"By back-integrating into the value chain, the CMO will ensure it can not only fill capacity, but the large number of chemical steps performed in the same facility will also allow greater process improvement opportunities," said another.

Similarly, by moving into the final product, the peaks and troughs of CMO capacity utilization can be smoothed out to some extent through the absorption of excess capacity for own product manufacturing. But tempting as it might be to adopt a one-stop-shop strategy, some experts suggested that this may not be the best solution because by trying to be everything to everybody, you run the risk of failing, which isn't good for a CMO, its customers, or patients. Experts told us:

- "Though there is pressure for CMOs to acquire more competencies and move to formulation activity and vice versa, the preferred approach is to hold your hand up and say 'we're not specialists in everything, but what we focus on, we are experts in.'"
- "The one-stop-shop approach from API to formulation is not essential either. We do not attribute more value in the API and drug product being under the same roof."
- "If there is someone who can do everything, then great – but no one has managed this yet."

In summary, to take advantage of the favorable industry scenario of rising consumption, steady innovation and a dynamic outsourcing sector, CMOs will need to offer a technological edge, while at the same time remaining flexible. They must study trends to be in a position to adapt and move with the industry, and be big enough to stand out from the crowd, but not so big that they become difficult to work with. The next five years will present both risks and benefits, but it may well be that fortune really does favor the bold.

Matthew Moorcroft is Vice President at Cambrex, New Jersey, USA.

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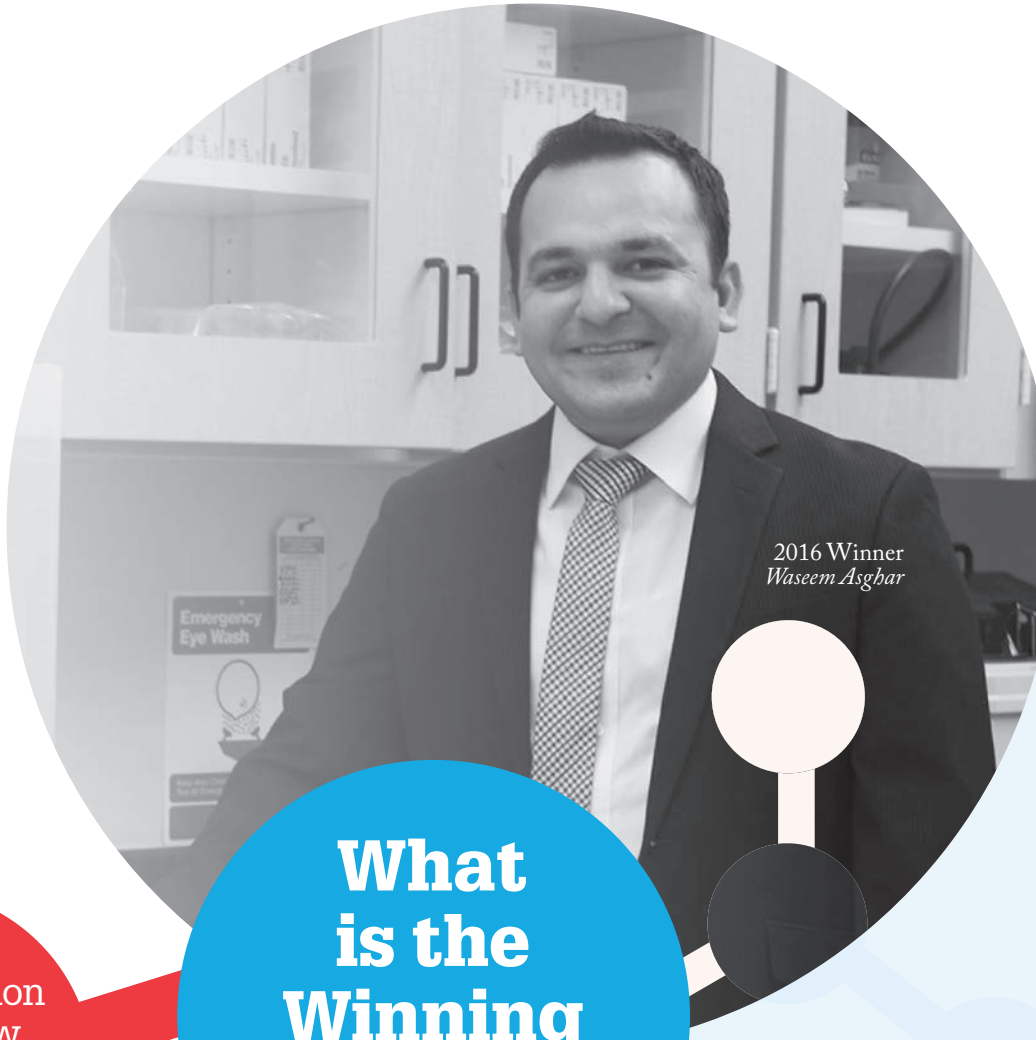

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The Importance of a Manufacturing Strategy: Lessons Learned with Steve Lam

For some companies, bioprocessing is a well-oiled machine. For others, it's a car crash capable of derailing a product launch by months.

By Stephanie Sutton

Commercial-scale bioprocessing is an art. Successful biopharma companies have perfected it through repetition and the implementation of new biopharma technologies. And so, manufacturing can be considered 'easy' compared with the trials and tribulations of drug discovery and clinical trials, particularly when product development follows well-established methodologies and a well thought-out manufacturing strategy. According to Steve Lam, Senior Vice President of Patheon's Biologics Business, considering your manufacturing strategy early on in development pays dividends down the line – and yet it is something that many small (and large) companies fail to do. Here, Lam recounts the lessons he has learned over almost three decades in biopharma.

Applied science is the most engaging

With a degree in physical chemistry, you may have expected me to pursue a career in small-molecule drug development rather than biopharma. It all started at Argonne National Laboratories – where my dad worked. I attended an open house at the laboratory as a child; kid friendly experiments and freezing things with liquid nitrogen are very effective ways to engage children in science. Eventually, I chose a degree in physical chemistry and in my last year of college I was preparing to do a PhD. All of my work up until that point had been in physical chemistry, but then everything changed. I was researching the base energy state of uranium, which was fascinating, but my advisor told me that it wouldn't be applied for around 20 years or so... That horizon was too far away in my mind. So, after college, I opted to go into industry and I started my career at Armour Pharmaceuticals. The timelines in pharma development are long too, but it is certainly very much applied and very worthwhile. Much of my career was spent at Amgen, so despite the focus on physical chemistry my career has been based around biopharmaceuticals.

A positive work atmosphere and teamwork can boost drug development

Initially, I started out in clinical manufacturing at Amgen, but over time I had the opportunity to move into various functional departments within the company. The company went through a significant transformation in a relatively small space of time – and I was excited to be able to contribute. Early on in my career, I had the opportunity to lead a quality control unit for the company. At the time, the unit was used for quality control for the majority of the company (which was smaller back then) so product samples would be sent to the unit for testing. As the company grew, it was decided that products would instead be tested where they were made. The decision created a significant need for change in the organization and I was involved in developing the leadership team in quality control. Importantly, we did this in a very positive way. We didn't lay people off and we focused on creating a positive environment for the company.

I also had the opportunity to manage plants. One challenging project was transforming a single product, microbial commercial manufacturing plant in Colorado into a multi-product facility. It was a huge engineering project because the new product was a mammalian product – the facility also had to be multi-host. It was a big change. Eventually, I progressed into global operations planning, contract manufacturing and operations. By the time I left in 2016, I was Vice President of Operations.

One of the most fundamental lessons I learned was the importance of teamwork. The term "teamwork" is often bandied about by employers – and I'm sure everyone thinks they understand the importance of teamwork – but it is not always implemented well. From a personal point of view, I believe that teamwork is instrumental in our industry. Discovering, developing and manufacturing biologicals is a very complex undertaking and requires many different disciplines. In some pharma companies, employees work in silos, and in my experience this means that things can take a little longer – and sometimes be unsuccessful. At Amgen, there was a team structure that brought diverse people together – and the effect was almost magical. By bringing different skillsets to teams, hurdles were usually overcome quickly. Teamwork was applied to everything, from drug discovery, through to development, and even work in the main factories. I still believe in the importance of teamwork. In today's biopharma industry there is a need to be more nimble and flexible, which is much easier if you have a cross-functional team of experts collaborating.

Understanding what you want is the best manufacturing strategy

When it comes to commercial biopharmaceutical manufacturing, one of the key lessons I have learned was the value of really understanding your manufacturing strategy early in your product's development lifecycle. At first, Amgen only had a handful of commercial products, which mostly used recombinant proteins. In time, the portfolio expanded and production processes began to rely on antibodies, which were more consistent and allowed for more efficient manufacturing.

Even when working with recombinant proteins, there was always a clear view of what a product would look like once it was commercialized, and this was used to extrapolate what a product needed in terms of manufacturing. Very early on, it would be decided what indication a product would be used for, what the patient population would be, and what the final presentation would look like. This meant that other key aspects could

also be addressed early on. For example, what does the unit cost need to be and how can we achieve this? What volume of drug is required? What is the best equipment and scale? If a product is expected to be a blockbuster, it provides greater confidence about implementing a 20,000-liter scale, stainless steel process. A niche product, on the other hand, may require a more flexible capacity solution. Overall, a well thought-out product and accompanying manufacturing strategy allows you to make key decisions around manufacturing with greater certainty, and better prepare your product for market.

Now that I am working at Patheon, a leading contract development and manufacturing organization (CDMO), I understand more than ever why early product and process knowledge is so important. All too often, companies – particular those at an early stage – have not thought about commercial manufacturing needs and whether their early-stage process is ultimately the best method for their product – or whether it will work on a large scale. For small, early-stage companies, funding is usually limited, which means they are often rushing to generate results in time to receive more funding. These companies are often so driven by results that they overlook key opportunities to stop and evaluate decisions that will guide and facilitate commercial manufacturing. The danger is that a company will make it to Phase III, and then suddenly realize that a crucial processing change is needed, which will impact timelines – and increase costs.

For some customers, we have been forced to backtrack and evaluate whether their processes are well understood. How do the process attributes affect the quality attributes? Are those well-defined? If there are gaps, they need to be filled to help ease the regulatory and commercialization process.

It's good to have a new perspective

Amgen was a fantastic company to work for, and I am particularly proud that I was able to see the company grow so much. In time, I found myself interested in returning to a smaller, startup environment because I missed the entrepreneurial, all-hands-on-deck atmosphere. And that's why I ultimately joined Patheon in February 2016. I find it exhilarating to be working with so many different clients and have responsibility for the four sites that manufacture biologic drug substance, as well as process development.

"As part of a manufacturing strategy it's important to review new technologies."

Successful, established companies tend to find manufacturing relatively straightforward because they have gained experience along the way. When I first started at Amgen, some of the plants were running at low run-rates and there weren't many commercial products. As the pipeline developed, the run rate increased and the company became much better at manufacturing because of repetition – processes began to run consistently and all products began to follow similar commercialization pathways. The company also implemented the right processes, systems and training to operate at a high capacity utilization and avoid errors. At Patheon, I work with companies of all shapes and sizes, including start-ups and virtual companies. Projects can arrive in very different stages – some are very advanced and have been well thought-out, others are very early stage, and some are advanced but still missing crucial process development. Overall, you gain a perspective that you just can't see in a big biopharma company – and it's very rewarding to optimize so many different processes and aid with product development.

New technologies can lead to better processes

The biopharma industry has changed significantly since I first started out and it's been exciting to have a front row seat. Over the last 20 years, there have been real changes in cell culture titers, particularly for antibodies. When I first started, 1 gram per liter was considered a good titer, but today companies are regularly pushing 4 or 5 grams per liter. The changing titers, as well as product indications and demand, have led to some big changes in upstream bioprocessing; most significantly, companies no longer need huge, 20,000 liter bioreactors because a 2,000 liter bioreactor can get the job done. Downstream processes, however, are still very large and there are questions about how these can be reduced. I've seen some exciting work in this area, including innovations in membrane technology, harvesting technology, and continuous processing. These advances have been taking shape for many years, but the serious developments were placed on the backburner while the industry was chasing titers. Now that we have titer, it's time to look at the bottlenecks downstream, and to examine how to break them.

New technologies are emerging all the time to help facilitate bioprocessing, but some companies appear oblivious... As

part of a manufacturing strategy, it's important to review new technologies. If you haven't thought about your manufacturing strategy early enough, then the tendency is to try and use a platform process. Platform processes have their advantages (easy to implement), but users also lose the opportunities for greater efficiencies and economies offered by state-of-the-art processing technologies. If you have a product that is expected to be a blockbuster, then big stainless steel tanks will give the lowest unit costs. If you have a niche product with uncertain future demand, then stainless steel can be risky – single-use technologies and multiplexing are usually worth considering. Single use and other flexible technologies can also be an effective bridging strategy while you try to better understand demand for your product. In some cases, companies adopt a first generation process, with the aim of introducing second and third generation processes as time goes on – and gradually improving the process.

Science isn't an issue, but cash is

Manufacturing is a very repetitive process and the more you do it, the better you get. Scientifically, we now know a lot about manufacturing and bioprocessing, and if a company is struggling with a problem then there are many external experts and CDMOs that they can turn to. Science is also advancing in terms of drug discovery. We are seeing an exciting transition to the cell therapy space with CAR-T technologies and gene therapies, and conversations are moving from therapies to cures.

Science and manufacturing prowess continue to advance, but the industry is struggling in terms of funding – a significant problem for early-stage companies – and the cost of medicines. These are the challenges of today but also the future. What happens when medicines are developed that people cannot pay for? The new, groundbreaking treatments coming through the pipelines come with high costs, but it will be a onetime upfront cost, as opposed to ongoing therapy, which may require daily pills or weekly injections, as well as medical interventions and hospitalization. It is a public policy challenge – and how the situation plays out will affect the future of our industry. While we cannot directly address this in a manufacturing strategy, we can focus on making high quality products in the most efficient manner possible.

Remaining (Pharmaco) Vigilant Post-Brexit

Pharmacovigilance has become increasingly integrated across the EU, but the Article 50 clock is ticking. A Brexit deal that fails to deliver continued close cooperation between the UK and the EU is not an option for patients.

By John Barber

On June 23, 2016, the UK narrowly voted to leave the European Union. Since then, the country's two major political parties – Labour and the Conservatives – have accepted the result as a binding commitment and have pledged to deliver Brexit. On March 29 this year, the government triggered Article 50, starting a clock that will stop ticking at midnight on March 28, 2019. And yet no detailed Brexit plans have materialized and, over the next two years, negotiations over both the terms of departure and a future relationship will need to take place. The vital practice of monitoring the effects of drugs after they have been licensed for use – pharmacovigilance – will also need to feature in both sets of negotiations.

Pharmacovigilance activities across the EU are highly integrated between marketing authorization holders and competent authorities. Moreover, the UK's Medicines and Healthcare products Regulatory Agency (MHRA) has been highly influential in developing pharmacovigilance science and practice in the EU. Brexit has the potential to significantly disrupt these activities, which could have adverse consequences for patient safety. One immediate consequence of the UK's intention to leave the EU will be the EMA's departure from its current location in Canary Wharf, London. Several cities across Europe are pitching for the right to host this prestigious agency and a decision should be made in October. But damage is already being done; morale is reportedly low amongst the agency's 850 staff, not all of whom will be willing or able to relocate – particularly the UK citizens who may lose their right to work elsewhere in the EU. This distraction may reduce the EMA's capacity to conduct its routine work and is highly likely to affect its ability to deliver on major IT projects, such as the upgrade of the Article 57 medicinal product database to the IDMP (Identification of Medicinal Products) standard. There will also be knock-on effects on Marketing Authorization Holders (MAHs).

The break up

Not only are the EMA headquarters set to leave London, but it also seems likely that the UK will not be part of the EMA post-Brexit, according to the UK Secretary of State for Health (1). Outside of the EMA, I can see two potential scenarios for how the regulatory framework in the UK may look from April 2019.

The first and, by industry consensus, the best option is for the UK pharmaceutical industry to continue to operate in alignment with the EU regulatory framework and to participate in EU regulatory procedures. In this scenario, the UK would aim to maintain alignment with current and future EU pharmacovigilance regulations, while also continuing to contribute to the advancement of pharmacovigilance science and practice. The use of the word "alignment" is key, as it implies that the UK will not be bound fully to follow these regulations and could adapt or ignore them depending on what the country considers appropriate. Alignment of the UK and EU regulatory frameworks would help to reduce the impact of additional costs and regulatory burdens relating to pharmacovigilance activities in the UK and EU post-Brexit. With respect to the Article 57 and EudraVigilance databases, the UK could benefit from continued access to both.

The second scenario involves the MHRA working independently outside the EU regulatory system. It may include a mix of alignment with some EU regulations, regulations from other agencies (for example, the FDA) and perhaps UK specific pharmacovigilance regulations post-Brexit. This model would be complex and would take time to set up, as the UK regulatory system is currently fully aligned to that of the EU. Under this model, access to the Article 57 and EudraVigilance databases would probably not be available to the UK.

With either model, retaining as many of the current arrangements with the EU as

possible is desirable to minimize additional costs and administrative burdens. In particular, this should include continued use of the EMA's Good Pharmacovigilance Practice (GVP) guidance. The UK, via the MHRA, has played a key role in the development and application of the EU's pharmacovigilance systems. Hopefully, this will continue, although any influence is likely to diminish post-Brexit.

What of the QPPVs?

Another problem for the pharmacovigilance community is the uncertainty surrounding the status of UK-based QPPVs (Qualified Person for Pharmacovigilance). To sell into the European Economic Area (EEA), each MAH requires the services of an EEA-QPPV, who is responsible for ensuring the safety of the company's products and compliance with its pharmacovigilance obligations. The EEA-QPPV must live and work within an EEA country and some member states also require a national QPPV (although not the UK). At present, it is estimated that there are a total of 1,358 QPPVs in the EEA – 153 of which are based in the UK. For these UK-based EEA-QPPVs, their futures are in question – not to mention their support teams in their QPPV offices. As a single entity, the community of UK-based QPPVs has a huge wealth of knowledge and experience of pharmacovigilance and has been instrumental in driving the development of the current European pharmacovigilance legislation.

It is highly unlikely, however, that there will be a role for UK-based EEA QPPVs post-Brexit – if it is a hard Brexit. At the end of April, the EMA and the Heads of Medicines Agencies (CMDh) issued notices that stated very clearly that some pharmacovigilance activities must be conducted from within the EEA (2,3). This includes EEA-QPPVs, and indicates that MAHs should start making arrangements to ensure compliance with this post-Brexit. MAHs may not be able to

A Third Option

By James Strachan

In January, the UK Prime Minister, Theresa May, set out the Government's 12 objectives for negotiations with the EU. In the speech, May emphasized; "What I am proposing cannot mean membership of the Single Market." Those words seemingly dashed industry hopes of the UK retaining its membership of the single market though the European Economic Area (EEA) and European Free Trade Association (EFTA): the "Norway model."

As a member of the EEA, the UK would retain access to the Article 57 and EudraVigilance databases, UK-based EEA-QPPVs could continue to work with MAHs, and the MHRA would continue to perform PSUR single assessments. Beyond pharmacovigilance, this model would eliminate the possibility of timely and expensive customs checks for UK exporters, as well as allowing drug companies to get EEA-wide marketing authorization.

May ruled out this model saying, "Being out of the EU but a member of the single market would mean complying with the EU's rules and regulations [...] without having a vote on what those rules and regulations are."

Whether this is a fair characterization of the "Norway Model" is debatable. Firstly, EEA/EFTA members are able to veto the incorporation of new EU legislation into the EEA. Secondly, Norway only implements around a third of EU law (1), most of which originates at various international organizations (2). Although the UK would lose influence and voting rights at the EU level, it would no longer be represented by a European Commission common position at the international level. The MHRA could thus become an independent member of bodies such as the International Conference on Harmonisation (ICH) – indeed, the MHRA reportedly made an application (3) – whose guidelines have been incorporated into the EMA's Good Pharmacovigilance Practices (GVP) (4).

The elephant in the room is immigration. For many of the UK's "Leave" campaigners, having to comply with the Freedom of Movement makes EEA/EFTA membership unpalatable. Yet Liechtenstein, a member of the EEA, was able to negotiate an opt-out to free movement through Article 112 of the EEA Agreement, which EEA members have the unilateral right to invoke – suggesting that room for maneuver may be possible.

What happens now is anyone's guess. With the recent election resulting in a hung parliament and May's leadership looking fragile, some are calling for a rethink of her Brexit strategy. Will this mean EEA? Who can say? But as March 30, 2019 draws ever closer, the EEA option may begin to look increasingly attractive as a transitional step towards a more permeant agreement that could be negotiated without Article 50's ticking clock.

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A Third Country: the View from the EMA

By Stephanie Sutton

In May, the European Commission and EMA published a notice to marketing authorization holders of centrally authorized medicinal products for human and veterinary use (1). The notice stated, "The United Kingdom submitted on 29 March 2017 the notification of its intention to withdraw from the Union pursuant to Article 50 of the Treaty on European Union. This means that unless the withdrawal agreement establishes another date or the period is extended by the European Council in accordance with Article 50(3) of the Treaty on European Union, all Union primary and secondary law ceases to apply to the United Kingdom from 30 March 2019, 00:00h (CET). The United Kingdom will then become a 'third country.'"

The notice reminds MA holders of certain "legal consequences" that should be considered – and a Q&A document has been released to help marketing authorization holders understand what they need to do to prepare for the deadline (2). Here is a selection of some of the points raised in the Q&A document:

- Marketing authorizations. If a UK company is a marketing authorization holder then it will need to transfer its marketing authorization to a holder in the EEA before March 30, 2019.
- Orphan designation. Orphan designation holders established in the UK will need to transfer their designation to a holder established in the EEA.
- Manufacturing sites. When the UK withdraws from the Union, medicinal products or active substances manufactured in the UK will be considered imported medicinal products or imported active substances, respectively.
- Batch release. MA holders need to transfer any UK-based site of batch release to a location established in the EEA.
- QPPV. The qualified person responsible for pharmacovigilance must reside and carry out his/her tasks in the EEA. The QPPV will therefore either need to change their place of residence and carry out his/her tasks in the EEA or a new QPPV will need to be appointed.
- PSMF. The MA holder will need to change the location of the PSMF to the EEA.
- SMEs. UK-based SMEs will no longer have access to financial and administrative assistance. The Q&A states, "In order to be eligible for financial and administrative assistance, companies must be established in the Union (EEA) and meet the definition of an SME".

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recruit new QPPVs and associated personnel to replace all those currently working in the UK. Free movement of UK-based QPPVs to remaining EU/EEA member required, or a transitional agreement.

Preparing for the worst

Since 2012, MAHs are required to maintain a Pharmacovigilance System Master File (PSMF), which describes the company's pharmacovigilance system. The PSMF should be located at the site where the EEA-QPPV is based, or where the bulk of the company's EU pharmacovigilance activities are conducted. It is generally an electronic document, so relocation from the UK is unlikely to be a concern for most MAHs. The PSMF concept is starting to be adopted by other agencies outside of the EEA, but unfortunately, this has resulted in some companies having multiple PSMFs. Hopefully, the UK will continue to accept the EU PSMF template and not require companies to develop a UK-specific document.

Over the last few years, there has been a concerted effort – through safety referrals (for example Article 31 referrals) and work-sharing assessment of Periodic Safety Update Reports (PSURs) – to reduce duplication of activities relating to assessment of emerging safety concerns and changes to benefit/risk profiles of established medicines. Previously, each national competent authority assessed PSURs submitted to them by MAHs. For generic products, they could receive multiple PSURs for a single active substance from multiple MAHs, but at different times. Work-sharing assessment changed this; a single authority now assesses the PSURs received from all MAHs across the EU, and all covered the same review period. The result is harmonized assessment and harmonized recommendations for labeling changes or other safety actions. In 2016, this was further streamlined and simplified following the introduction of the single assessment portal.

There is a big question over how these PSUR single assessment procedures will be conducted post-Brexit. It is not the EMA that conducts the assessment, but the national competent authorities. Of the approximately 1300 actives for which a lead member state for assessment has been assigned, approximately 16 percent have been assigned to the UK's MHRA – significantly more than any other competent authority. If the MHRA is unable to provide such assessment activities post-Brexit, the work will have to be reassigned to the other member states, which will pose two problems: first, it is not clear that the other member states will have the resources to perform this function in the initial post-Brexit period; second, member state competent authorities are paid to perform this assessment, so it could represent a significant loss of revenue for the MHRA. How will the budget hole be filled? Will it introduce new or higher fees for pharmacovigilance services?

At the time of writing, there are very few knowns and many unknowns regarding the impact of Brexit on pharmacovigilance but, as an industry, we must prepare for the worst. With luck and a fair wind, the negotiations – particularly those relating to pharmaceutical regulation – will progress smoothly and quickly so that the uncertainty regarding the future of pharmacovigilance in both the UK and the EU is limited.

Just before this article was published, the UK's general election was decided. The clear and unequivocal mandate that Theresa May sought has not been granted to her by the UK electorate.What is certain is that there is much work ahead for both MAHs and the competent authorities across Europe.

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Clinical Data Star

Sitting Down With... Elisa Cascade, President, Data Solutions at DrugDev, Washington D.C., USA.

When did you decide to focus your career on healthcare data?

When I started my studies at the University of Michigan, I set up my schedule with an eye towards taking all of the pre-requisite classes for medical school, but I was so interested in economics that I ended up majoring in it. Upon graduation as a pre-med economics major, I decided to look for a job as opposed to going to med school straight away. Unsurprisingly, healthcare consulting was a perfect fit for both of my interests and after a few years, I decided that I enjoyed the analytics around healthcare more than actually practicing healthcare. I then continued my career and education in the direction of data and analytics in healthcare, specifically in the medical technology space.

What moments in your career have made you the most proud?

One was my involvement in building and delivering a patient community called MediGuard, which provided safety alerts and updates on medicines. Over a span of 3 years, we grew from a pilot concept at Quintiles to delivering drug safety information to nearly 3 million patients. I was very proud of the direct benefit we were providing to patients by making them aware of potential drug-drug interactions.

Later, I moved to the physician community space by joining DrugDev. When I was first brought into DrugDev in 2013, we had just started hosting the Investigator Databank (a global collaboration platform for sharing investigator information), which at that point involved just three pharmaceutical companies. Today, this has grown to over 12 companies actively sharing data on our platform, both in the Investigator Databank and now in TransCelerate's Investigator Registry. When we started this journey around 4 years ago, companies seemed to be afraid of losing a competitive advantage in the area of study planning and site identification, but today we have yet to find a company that is not interested in data sharing.

"Today, the idea of patient recruitment support has become standard for clinical trial delivery."

How has clinical trial recruitment changed over the years?

With the increase in protocol complexity and more niche products and indications, finding eligible clinical trial subjects has required access to more data for evidence-based planning and decisions. When I first started my career, while data and analytics were commonly used on the commercial side of the business, industry wasn't really using data in clinical trial delivery. Today, companies rely heavily on healthcare data to select countries, estimate enrolment, and find the right sites and patients.

When we first started MediGuard in 2008, the idea of working directly with patients for clinical research resided primarily in the innovation department of pharmaceutical companies and contract research organizations. Today, the idea of patient recruitment support has become standard for clinical trial delivery, but I feel that more work is still needed to make it easier for patients to participate in clinical trials. For example, many patients still do not even know anything about how to get involved with a clinical trial…

You are one of the few women on our 2017 Power List…. Do you think there is a problem with women being recognized for their role in the industry?

I was very honoured to be named on the Power List! But yes, many women aren't recognized as leaders and do not advance into leadership roles. I think it comes down to personality and behavioral differences between men and women. It has been widely reported that women give themselves less credit and often receive less recognition for their accomplishments in comparison to men. They also feel the need to be 100 percent qualified before applying for a new position, whereas men will often go after a job they are only 60 percent qualified for – and assume they'll learn the rest on the job. It comes down to confidence.

What can be done to better support women in industry?

It is critically important for women to support one another and to encourage greater self-confidence about their accomplishments. Women need career path encouragement, a circle of mentors, a sponsor, networking opportunities, and a great support network. I find this is true not only for women who are just starting their career, but also experienced women, including myself, who also benefit from a peer's reassurance about their own abilities.

We seem to be heading in the right direction with schools focusing on STEM programs for girls, and companies offering women leadership programs and mentoring circles, but we can still do a lot more to remove barriers and support women and their career advancement. Not only is it the right thing to do, but it is also the profitable thing to do – McKinsey reports that companies with a female CEO or at least three women on the board or in the C-suite perform better than those without.

Any final thoughts?

Rolling off of topic of women in business, I would just like to add that I couldn't have accomplished nearly as much without the love and support of my husband and twin boys who are now aged 16. They truly motivate me to work hard, play hard every day.

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