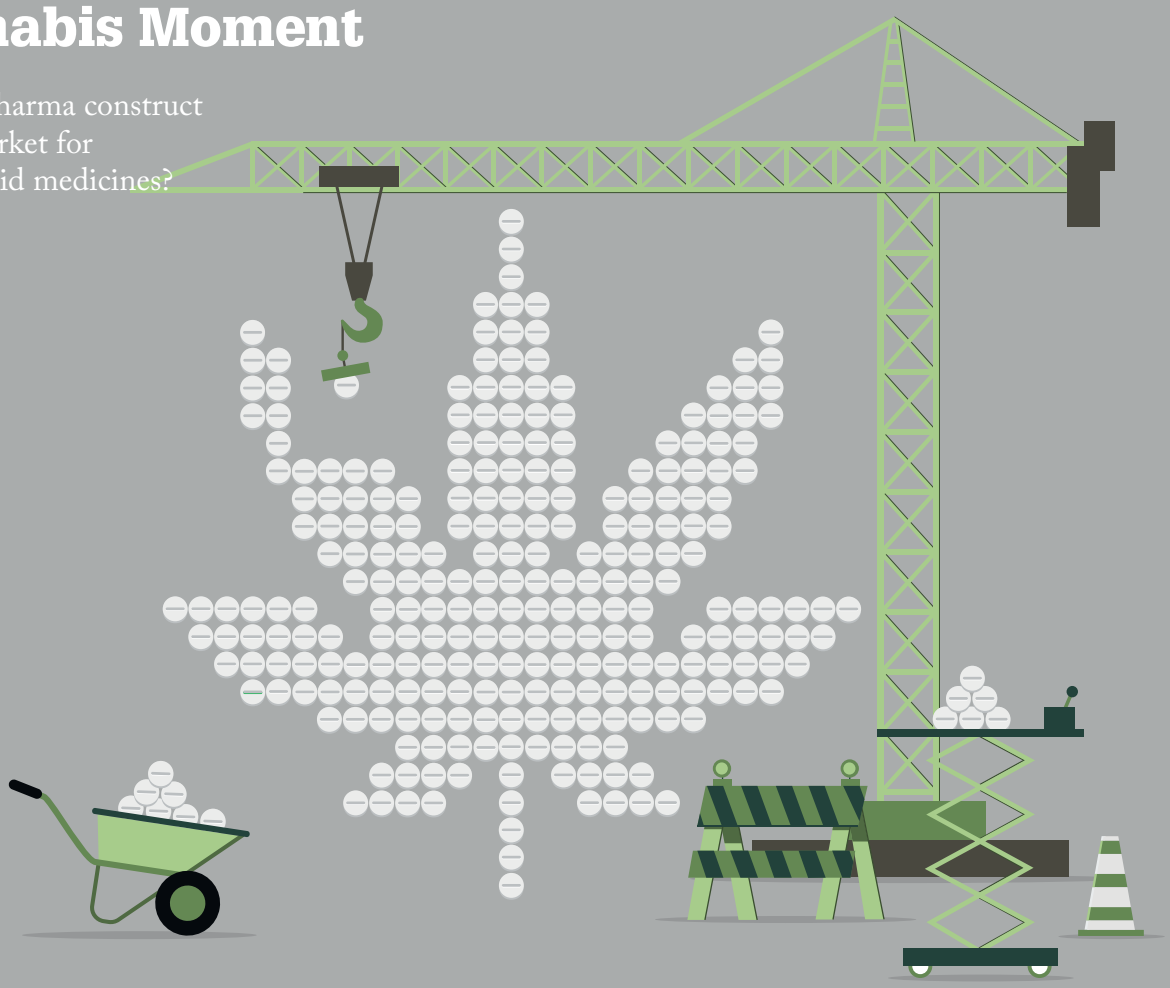
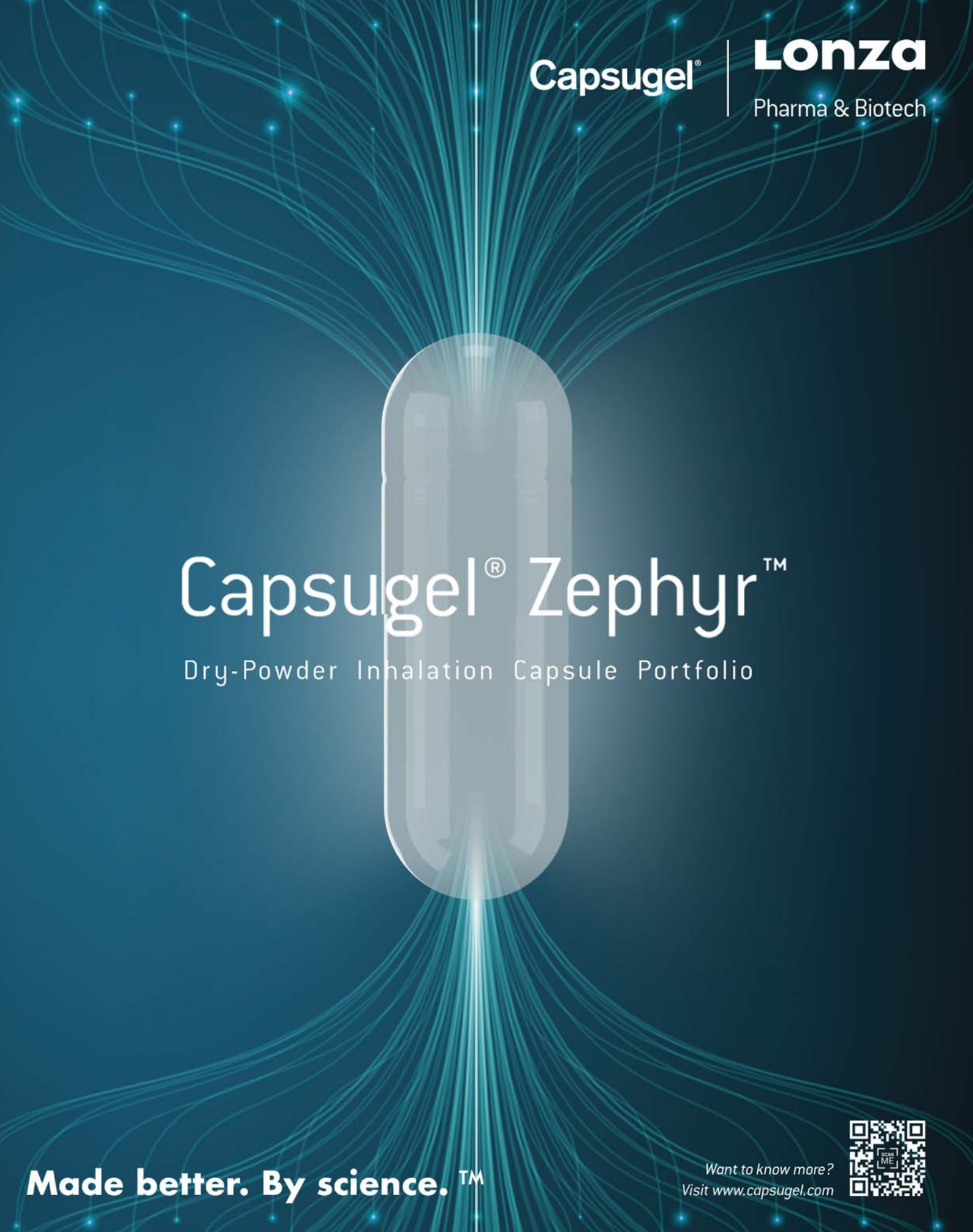
MAY 2019 # 53

the Medicine Maker™

Capitalizing on the Cannabis Moment

Can big pharma construct a solid market for cannabinoid medicines?

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SCAN ME

Online this Month

And for 2020...

The Medicine Maker 2019 Power List is now online at https://themedicinemaker.com/power-list/2019, celebrating the most inspirational professionals working in the pharma industry including Business Captains, Industry Influencers, Masters of the Bench and Champions of Change.

Do you agree with who was included (or not included) on the 2019 Power List? Now is your chance to shape next year's list: nominations are now open for 2020!

But there is a twist. For the past four years the Power List has compromised 100 names. For 2020, there will only be 60 names:

- 20 influencers in small molecule drug development
- 20 influencers in biopharmaceutical drug development
- 20 influencers in cell and gene therapy drug development

Who will earn a place on this exclusive list? Nominate now at https://tmm.txp.to/pl2020-noms. We accept nominations from all areas of the industry (from the bench, to manufacturing, to business leadership) and you can nominate yourself if you wish.

Nominations will close in early January 2020 and the final list will be published in April 2020. Email james.strachan@texerepublishing.com with any questions.

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Small – But Never Forgotten

A new publication will give the small molecule manufacturing community the attention and praise it deserves. Meet The Small Molecule Manufacturer.

The best-selling drugs in the world in terms of revenue are biopharmaceuticals. But when it comes to the amount of medicines most commonly used and prescribed, small molecules have large molecules completely beat. The over-the-counter medicine market is almost exclusively made up of small molecule products but, even when considering prescriptions, the most commonly used drugs are still small molecules. Lists vary depending on the sources used but, in the US, the most commonly prescribed medicines of 2018 were typically cited as levothyroxine, lisinopril, atorvastatin, metformin hydrochloride, amlodipine besylate, metroprolol, omeprazole, losartan potassium and albuterol. They are small molecules.

The importance of small molecules to global health is further emphasized by the World Health Organization's List of Essential Medicines, which includes general anesthetics, palliative care and pain medicines, antiallergics, antiinfectives, anticonvulsives, antimigraine medicines, immunosuppressants and cardiovascular medicines. What do most of the drugs on the list share in common? They are small molecules.

Small molecules also account for the lion's share of new drug approvals; over 60 percent of new drugs approved by the FDA in 2018 were small molecules. Innovation in small molecules is not dead. So it seems a little unfair that these workhorse medicines should be continually overshadowed by the latest biologics and "advanced" therapies.

And so, to celebrate the continued leaps and bounds in the small molecule arena, we are launching a new magazine in July. The Small Molecule Manufacturer will focus on the people, processes and technologies driving advances in the development and manufacture of small molecule drugs – as the name suggests. You can register to receive this new publication for free at https://tmm.txp.to/tsmm-regform.

"But does this mean that small molecules will be excluded from The Medicine Maker from now on?" – we hear you cry! Absolutely not. We will continue to report on the trends, technologies and personalities shaping all areas of the medicine making industry. Rather, The Small Molecule Manufacturer will serve as a special community for those working with an incredibly diverse and important selection of drug products that should never be forgotten.

Stephanie Sutton
Editor

Upfront

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

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

Solutions in... Nanoparticles

Why are spherical nucleic acids so exciting for drug development?

Invented in 1996 by the Mirkin Lab at Northwestern University, spherical nucleic acids (SNAs) have the potential to treat an array of diseases. Now, a group led by their inventor aims to optimize these nanoparticles for immunotherapies using a new machine learning technique (1). Chad A. Mirkin, Professor of Chemistry at Northwestern University, tells us more...

What are SNAs?

SNAs are nanoparticle structures made by chemically arranging nucleic acids (biomolecules essential for life) on a spherical nanoparticle core. Despite having no known natural equivalent, they are able to interact with living systems in various ways. Most notably, they enter cells rapidly, and in large quantities, and resist degradation by enzymes.

We've observed SNA activity in the brain, a commonly hard-to-access tissue, upon intravenous injection. In addition, they enter the skin, eye, lung, and lymphatic system when topically or locally administered. These properties have made SNAs attractive as gene regulation agents, and as structures for modulating the immune system, making it possible for them to be used as nucleic acid medicines for the last decade.

What can SNAs treat?

SNAs represent an exciting new class of nanomedicines and have a wide scope in terms of clinical applications. With their capacity to shut off gene and cellular activity, we hope to see more SNAs used as personalized therapies for genetic disorders, as well as some types of cancer. Since developing these nanostructures in 1996, seeing them used to their full potential has been a constant goal of mine! In 2011, I founded Exicure, a biotech startup which develops gene regulatory and immuno-oncology therapeutics based on SNA technology. We currently have treatments for psoriasis, spinal muscular atrophy, bowel and lung diseases, as well as ocular diseases in our pipeline.

What are the current advantages and limitations of SNAs?

SNAs are customizable – their size, core composition and DNA/RNA sequences can all be fine-tuned to produce myriad variations. The ability to introduce variability to the design parameters of SNAs means that millions of combinations are possible, all with differing compositions and structures.

It is not currently understood how the different structural parameters collectively influence biological function, and using traditional methods, it would be impossible to study large swaths of the possible combinations. This inspired us to devise a high-throughput method to synthesize large SNA libraries with thousands of candidates and rapidly analyze them to determine which parameters influence immunostimulation.

How will your newly devised machine learning technique help optimize SNAs?

Our machine learning models can analyze SNAs and identify how their structural

variation contributes to their efficacy and biological activity. Our novel technique highlights important properties of SNAs, such as their size-dependent ability to stimulate the immune system, which would otherwise be overlooked using more conventional methods. The high-throughput pipeline that we have developed also reveals the "interaction" effects between multiple features of SNAs.

How do you envisage SNAs being used over the coming decade?

SNAs provide a way to exploit what is known about nucleic acid recognition for medicine, without the limitations of linear nucleic acids. Almost all aspects of life derive from nucleic acids, so nucleic acid therapeutics have massive potential! Furthermore, nucleic acids are signals that can be recognized and exploited by the immune system to trigger an immune response. By using nucleic acids, we can target genes linked to disease and immunological receptors in ways to stimulate or suppress immunity. While a few nucleic acid therapeutics have been approved in recent years, issues surrounding their delivery have prevented these therapeutics from reaching their full potential. We believe that SNAs hold the key to not only the challenge of delivery, but also of potency in the way nucleic acids are recognized and processed by the targeted cells and receptors.

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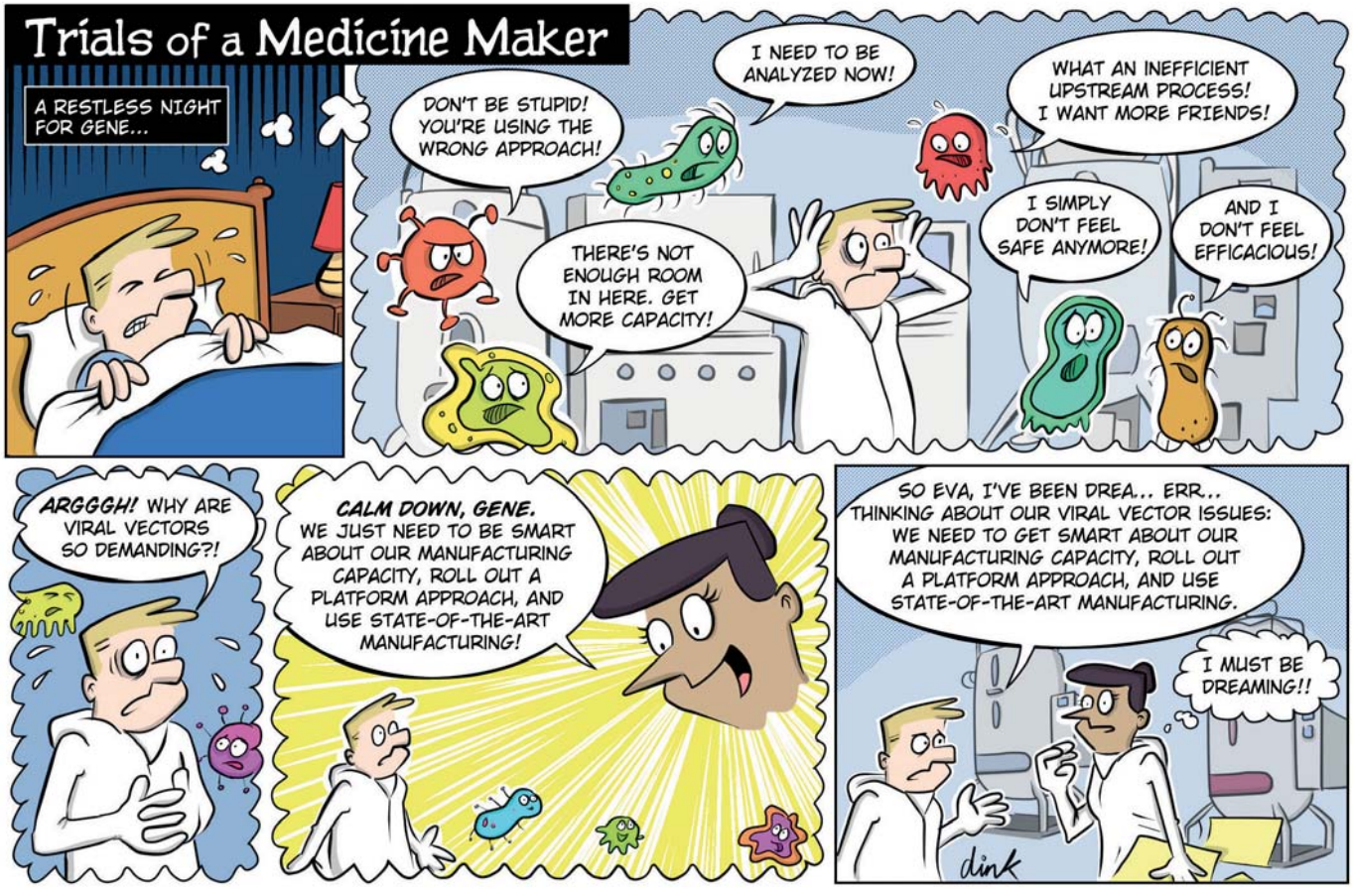

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2023: Prices and Predictions

How will the industry shape up over the next five years?

GRINDING TO A HALT?

DESPITE BEING FORECASTED TO GROW BY

$1.5 trillion by 2023

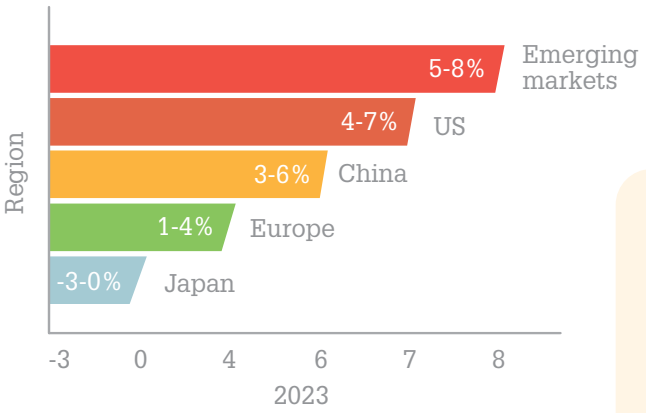
...the annual growth rate of the pharmaceutical market is set to slow over the next five years from an average of...

6.3%

...TO A PREDICTED GROWTH RATE BETWEEN

3% & 6%

GROWTH BY REGION



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AREAS TO WATCH

CRISPR -Cas9

Growth at a CAGR of **33.26%** between 2018-2023

Total market size expected to reach **$3.1 billion** by 2023

Pluripotent stem cells

Regenerative medicine market was worth **$28 billion** in 2018

Will grow to over **$81 billion** by 2023 - a CAGR of **23.3%**

Neglected diseases

5–10 new products to be launched in the next ten years

Neglected tropical diseases (NTDs) affect **more than a billion people across 149 countries** and cost **upwards of a billion dollars per year**

Continued investment by international organizations and philanthropic organizations could help to **eradicate at least one neglected disease by 2020**

Artificial intelligence, machine learning and deep learning programs

CAGR **48.2%** between 2018 and 2023

Total market size expected to reach **$10.88 billion** by 2023

Treasures of the Deep

Could aquatic bacteria hold the keys to bolstering our drug pipelines?

On a rocky shore in northern Portugal, researchers from the University of Porto have been busy collecting heaps of brown seaweed. Their purpose? To explore the bioactivity of the Actinobacteria found within it.

Actinobacteria, a phylum of Gram-positive bacteria, are ubiquitous in soil, freshwater and marine environments, and are clinically used for many antibiotics, as well as anticancer and antiinflammatory agents. In fact, more than half of the 20,000 microbe-derived drug candidates in development stem from the terrestrial species of the bacteria. But aquatic Actinobacteria haven't received as much attention.

"The diversity of the natural world is unparalleled. The adversities presented by their environments forces living organisms to adapt mechanisms of defense, which often results in the production of compounds with useful bioactivities," explains Maria de Fátima Carvalho, Principal Investigator at the Interdisciplinary Centre of Marine and Environmental Research of the University of Porto.

One of Carvalho's interests lie in the isolation of Actinobacteria from diverse sources so rather than focusing on the bench, she went to the coastline in pursuit of new therapeutic molecules (1). The team investigated cultivable Actinobacteria associated with Laminaria ochroleuca seaweed and were able to recover 90 isolates. 45 of the strains identified were capable of inhibiting the growth of Candida albicans (an opportunistic yeast which causes candidiasis) and Staphylococcus aureus, and a further 28 displayed inhibitory effects on breast carcinoma and neuroblastoma cell lines. The team also discovered two strains that produced bioactive compounds not previously featured in common databases of natural products, and are now investigating them with increased scrutiny to determine if they are indeed novel chemical entities.

"Up to 90 percent of drugs are rejected in preclinical drug screening," says Carvalho. "Until now, no one had characterized the Actinobacteria in L. ochroleuca. Our findings are an exciting step in the right direction. The more drugs candidates available and the more strains of Actinobacteria we discover to feed drug development channels the better!"

Carvalho and her team intend to explore Portugal's waters further in the search of other species of seaweed and new communities of Actinobacteria.

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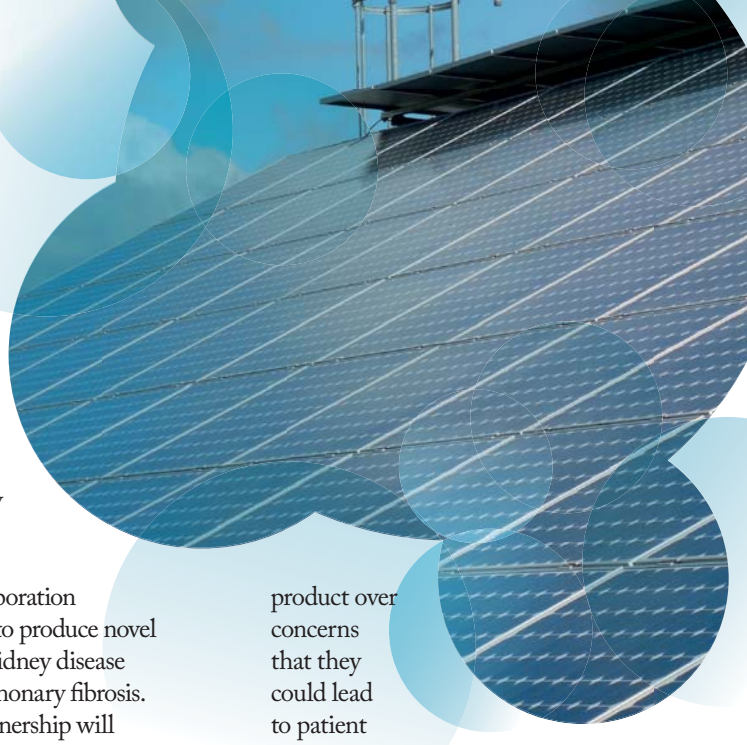

Business in Brief

Social responsibility at its finest, AI partnerships, and a crack down on vaccine manufacturing malpractice... What's new for pharma in business?

Corporate Responsibility

- In an attempt to cut its CO_2 emissions, Novo Nordisk has invested in a 632-acre solar panel installation in North Carolina. The installation covers the same area as 500 football pitches and will help the company reach its goal of achieving 100 percent carbon neutrality by 2030. The project will provide the company's entire US operation with energy by 2020, severing the company's ties with traditional energy sources.
- Abbvie has pledged $40 million to rebuild a school based near its headquarters in North Chicago. The donation to The Neal Math & Science Academy was the last in a series of awards given from the company's $350 million tax rebate and will serve to transform the school into a "21st-century learning space."

Artificial Intelligence

- With the intention of exploiting AI to accelerate the drug discovery process, Janssen has partnered with Iktos to use the company's AI powered technology. The collaboration will allow the two companies to share their expertise in deep generative models and the prediction of small molecule activity. Iktos has also recently announced other newly formed partnerships with biopharmaceutical companies in pursuit of novel compounds using in silico methods to identify and design them.
- BenevolentAI has entered into a collaboration with AstraZeneca to produce novel drugs for chronic kidney disease and idiopathic pulmonary fibrosis. The long-term partnership will see BenevolentAI combining their target identification platform with AstraZeneca's genomic and clinical trial data. The companies are confident that their alliance will lead to a greater understanding of the mechanisms underlying these diseases.

Recalls

- Torrent Pharmaceuticals recalled 104 lots of Iosartan (amounting to 1.07 million bottles of the drug) in April over concerns that they contained cancer causing impurities. The Indian pharmaceutical company recalled 36 lots of losartan potassium and 68 lots of losartan potassium/hydrochlorothiazide tablets, according to the FDA. In the weeks prior to the mass recall, the FDA had called for doses of Iosartan to be tested to identify whether they contained any of the impurities discovered in other blood pressure medications. Iosartan is now one of a dozen drugs to be recalled over safety concerns calling into question inspection processes at international plants.
- Fentanyl, the frequently used (and addictive) pain relief medication has been a popular topic of conversation of late in US news media. Now, mismarked packaging of the drug has led Alvogen to recall two lots of the product over concerns that they could lead to patient overdoses. The patches were labeled as containing 12 mcg/h, when in reality they contained more than four times that amount (50 mc/h). No adverse effects have been reported but Alvogen recommends that patients who are using mismarked patches immediately discontinue their use.

Vaccines

- Dengvaxia, Sanofi's vaccine for dengue fever, has, again, faced restrictions from the FDA. A regulatory committee ruled that Dengvaxia can only be used in patients who have contracted dengue before and in areas where the disease is endemic, limiting its use to the US territories of Puerto Rico, the US Virgin Islands and Guam.
- Chinese drugmakers who are found guilty of making or distributing counterfeit vaccines will feel the full force of the law after a second draft of legislation was released. China wants to root out malpractice through tougher penalties for perpetrators. The new legislation will allow victims of vaccine counterfeiting to seek compensation if they experience adverse events (including death, organ injury or serious disability) due to immunization with such products.

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

(Block)chain Reaction

Blockchain could be one solution to the saleable returns verification aspect of the US Drug Supply Chain Security Act.

By Heather Zenk, Global Secure Supply Chain Operations, AmerisourceBergen, USA.

In my view, one of the most exciting aspects of blockchain is its potential to revolutionize the way the pharmaceutical industry exchanges data. Electronic medical records, clinical trial management, supply chain, and scientific data sharing could all benefit from a distributed blockchain system, where data is managed by a cluster of computers, rather than any single entity.

One example of blockchain's applicability in the pharma industry is the Drug Supply Chain Security Act (DSCSA) Saleable Returns Verification requirement in the US. By November 27, 2019, when a pharmacy returns a product, the distributor will be required to verify that the serial number on the bottle is the same as the serial number the manufacturer applied to the package, before it can be restocked and resold. In today's environment, the distributor would have to connect with a manufacturer on a one-to-one basis. My own distribution company, AmerisourceBergen, works with 450-plus pharmaceutical manufacturers. With our existing systems, the new requirement would mean taking the serialized bottle from a pharmacy, scanning it to assess which manufacturer it belongs to, and then asking them whether the serial number is valid – for 15 million units. A mammoth task!

What we need is a system that tells us which manufacturer we need to contact. At the moment, that decision lies in the hands of the person trying to process the return. A larger system could scan the serial number, which has a global trade identification number called G10, and use a directory (akin to a phone book) to understand which manufacturer the product belongs to. We started to look into this, but issues arose when we considered how to manage the "phone book." Keeping it up-to-date would involve many manual interventions, such as phone calls, emails and so on. We also realized that we would run into problems if different manufacturers used different technologies. And that led us to consider a new avenue: blockchain.

Blockchain would allow us to communicate with a community or pharmaceutical ecosystem in a non-

"There are a lot of opportunities with the technology, but the industry won't convert for the sake of it. Blockchain must be cleaner, faster and safer."

direct way. The request would go into a pharmaceutical blockchain that could use the lookup directory to request information appropriately from the right manufacturer.

To implement blockchain, we've been working with a company called Chronicle through their pharmaceutical working group: Medileger. But a key question is: what if companies don't want to engage with blockchain technology? In the end, we've told our trading partners that if they don't have a means of interacting with the new system, we won't be able to process their return, which would mean that two percent of their products would need to be taken out of the supply chain.

I would urge pharma companies to seriously consider investing in blockchain. Traditionally, manufacturing and R&D, not data exchange, are key priorities for pharma companies. But if they can't do basic data exchange then wholesalers can't receive and process their information. We're beginning to see a significant shift as companies understand that, if data doesn't move when products move, we cannot deal with those products in the supply chain. As the regulatory environment changes with DSCSA and global serialization requirements, more companies are seeking to change their methodologies and enhance their abilities in data exchange. Blockchain is emerging as a tool that we can use to move a significant amount of data – and it can be replicated across the trading partner and blockchain environment, without creating a multitude of different databases or storing information separately. It allows a large company, like ourselves, to keep all of our data in one location that we can access efficiently and effectively.

Moreover, the industry has been forced to seriously contemplate the strength of its security systems given that numerous pharma companies have been hit with ransomware attacks in recent years. Merck, Sharp and Dohme had to halt production of new drugs in 2017 because of such an attack. As the industry looks for ways to shore up its IT systems, blockchain has risen as a potentially useful option. And with specific use-cases emerging, I believe companies will begin to see the real opportunities.

We used to say the pharma industry adoption curve was eight to 10 years for new technologies but, providing that regulators get on board, I think that blockchain could be mainstream in pharma in just three to five years. There are a lot of opportunities with the technology, but the industry won't convert for the sake of it. Blockchain must be cleaner, faster and safer – and I believe that, as use increases and we iron out the kinks, it certainly will be.

The Killer Combo

A longer-lasting strategy to rejuvenate existing antibiotics with synergistic combinations is likely to be an integral part in the development of treatments against antibiotic resistant pathogens.

By Anthony Coates, Professor of Medical Microbiology, St George's, University London; Founder and Chief Scientific Officer, Helperby Therapeutics.

Bacteria are constantly evolving to be antibiotic resistant and are a real and present danger to our ability to treat common infections and carry out standard medical procedures, including organ transplantation, major surgery and cancer chemotherapy, among others. According to the O'Neill UK government AMR report (2016), global deaths from AMR may reach 10 million per year by 2050, which is more than cancer and diabetes combined (1).

Innovation in both the short and long term is essential if mankind is to keep pace with ever smarter and deadlier microbes. The fight to outsmart infection falls broadly into rapid diagnostics technology and targeted treatment strategies involving new and updated antibiotics.

"Innovation in both the short and long term is essential if mankind is to keep pace with ever smarter and deadlier microbes."

But the pace of discovery and production of new chemical entities (NCEs) hasn't been so promising and has failed to keep pace with the unpredictable rate of bacterial

evolution. In fact, big pharma has mostly ruled itself out of the antibiotics game. The high cost of creating a new chemical entity and the low market price of new antibiotics deters large pharmaceutical companies, leaving the fight for antibiotic survival with the small biopharma companies, in what is the most urgent field of drug development. But small biopharma companies, even those which reach the market, struggle to sell NCEs. This is because, under present conditions, the market will not accept a price per course which will reimburse the high cost of developing an NCE. For example, if the cost of developing an NCE is say $200-500 million and the maximum unit price of a course of the NCE is $1-2000, it is difficult to make a reasonable profit. This conundrum is illustrated by Achaogen's filing for bankruptcy, in spite of reaching the market with an FDA approved NCE. Other small companies have and will survive in the market with NCEs, but achieving the equivalent profitability to successful blockbusters in other medical fields looks to be remote at the moment.

An alternative to the traditional pharma model is to use combinations of antibiotics. This is a route used to reduce the emergence of resistance in diseases such as tuberculosis, malaria and AIDS. Curiously, combinations (excluding those with beta-lactamase inhibitors which do not prevent resistance unless the inhibitor also has potent antibacterial action) are not often approved by the regulators for common bacterial infections. However, combinations hold the potential for a longer lasting, lower development cost, and lower price per course market solution. This strategy is based upon employing synergistic combinations. Simply, an old drug already in the market (called an antibiotic resistance breaker (ARB)) is combined with an old antibiotic also on the market. The ideal combination of drugs boost each other, which is known as synergism. This route re-uses old antibiotics by boosting them to overcome mutations developed by bacteria-conferring resistance. ARBs work in many different ways, including by facilitating the penetration of bacterial cell walls to allow existing antibiotics to work more effectively.

"The pharma industry is responsible for countless groundbreaking therapeutic innovations, but it will all be wasted if we ignore the growing issue of antibiotic resistance."

The ARB rejuvenation process can be performed repeatedly with different combinations of existing antibiotics. These new combinations can restore the original potency of existing antibiotics, against both Gram positive and Gram-negative bacteria. A small antibiotic biopharma called Helperby Therapeutics has been developing combinations for 15 years and has shown that some combinations have unique synergistic mechanisms of action that differ from other antibiotics in clinical use. Helperby Therapeutics has already completed a Phase I clinical trial and is Phase II ready with the first combination of azidothymidine (AZT) and the so-called last resort old antibiotic colistin against highly resistant carbapenem-resistant pathogens.

The World Health Organization has identified three multi-drug resistant species of bacteria which they classify as critical priority (2). These are all carbapenem resistant and require the immediate development of new treatments. The bacteria are called Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacteriaceae.

Multi-drug resistant bacteria pose a particular threat in hospitals, nursing homes, and among patients whose care requires devices such as ventilators and blood catheters. But we also need longer-lasting strategies. In my view, rejuvenating existing antibiotics with synergistic combinations should be an integral part of the fight against drug resistance. These strategies, combined with progress in the areas of prevention and diagnostics, are crucial to preserve a world where simple infections do not routinely kill healthy people. The pharma industry is responsible for countless groundbreaking therapeutic innovations, but it will all be wasted if we ignore the growing issue of antibiotic resistance.

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Choosing the Right Excipients for the Right Job

When it comes to formulation, many choices should be carefully considered – and regulators expect excipient selection to be justified.

The average timelines and costs of bringing a new drug to market vary depending on who you speak with, but are generally in the range of 10 years and over $2 billion, respectively. The broad hurdles of drug development are considered, but a topic that receives far less attention is formulation, including the choice of excipients.

The right excipients can reduce manufacturing costs, improve shelf life and stability, and enhance the patient experience. The competitive contract development and manufacturing landscape has given rise to CDMOs who hold impressive knowledge and know-how in terms of applying good scientific common sense in selecting the most appropriate excipients for the job at hand. Here, we speak with Rob Harris, Chief Technical Officer, Oral Drug Delivery, Catalent, UK, to find out more about the latest trends and drivers in the excipient field.

How have excipients improved over the last decade?

For some of the solvent excipients, such as oils and PEGs, greater purity has been a major improvement. Even low levels of impurities (for example, peroxides and aldehydes) can have a significant detrimental effect on drug stability. Also, reactive impurities can cause cross-linking of gelatin shells, affecting disintegration properties.

Better functionality for excipients has been another improvement. For instance, powder flow is an extremely important property for processes such as tableting and hot melt extrusion, so excipients that can improve powder flow for "difficult" powder blends are of interest to formulators. These can be excipient grades with particular particle size and shape to provide good flow properties or co-processed materials (for example, silicified microcrystalline cellulose), which offer similar advantages.

Indeed, co-processed materials – which combine the properties of two or more separate excipients into one – have become more widely available. These provide formulators with a single, multi-functional excipient option (for example, LudiFlash) that can help reduce development time and cost, certainly during early drug development.

Easy-to-prepare products, such as coating preparations for tablets (for example, Acryl-EZE) are now also available and can cut down on processing time.

What trends are driving innovation in excipients?

The number of poorly water-soluble compounds emerging from drug development pipelines is increasing year-on-year. Thus, there is a constant battle to develop suitable formulations for these poorly soluble drugs to allow administration and good bioavailability. Excipients that can enhance the solubility of otherwise challenging compounds are of great interest to formulation scientists. Non-ionic surfactants (for example, Vitamin E TPGS and Kolliphor RH40) are becoming common ingredients in pharmaceutical formulations. So too are polymer excipients that can be used to produce amorphous solid dispersions through spray drying and hot melt extrusion, such as PVP, HPMC and HPMC-AS and block co-polymers. Mesoporous materials with particles that have extensive internal surface area are also gaining popularity. It is possible to trap poorly soluble drugs in the amorphous state within the narrow passages in these particles and, hence, improve the solubility of the drug in aqueous media.

"The number of poorly water-soluble compounds emerging from drug development pipelines is increasing year-on-year."

Regulators are now encouraging and demanding the development of more pediatric versions of medicines, so it has become a key area of focus for the industry – with a subsequent influence on the excipient space. Ease of swallowing and palatability are essential requirements for patient acceptability and, therefore, excipients that can offer benefits in these areas are useful aids for formulation scientists. A number of excipients with attributes well matched to pediatric formulations are now available; for example, fillers and disintegrants that provide good "mouth feel" for orally dispersible tablets and coating materials that prevent premature release of the drug in saliva (for taste-masking).

How can formulators ensure they choose the "right" excipients?

It's extremely important to consider your choice of excipients – and have clear reason for their use. All formulation scientists should have a thorough understanding of the attributes of excipients used for a given type of formulation, and when certain materials should be used in preference

"All formulation scientists should have a thorough understanding of the attributes of excipients used for a given type of formulation."

to others. In all regulatory submissions, the reviewers expect a rationale for the selection of excipients, including the amounts used. Different grades of the same excipient can have marked effects on the desired behavior of a formulation.

Formulators should also consider:

- Compatibility with the drug substance to ensure that there is no undesired interaction between the drug and the excipient that could impact the stability and shelf life of the product. A drug-excipient compatibility study is normally one of the first activities undertaken for any formulation development program.
- Moisture content of the excipient – if the drug substance is moisture-sensitive (for example, use of an anhydrous grade versus hydrated).
- The drug substance may be sensitive to trace amounts of reactive impurities. Due care should be taken to use suitable types/low-impurity grades of excipients for such drugs. Low-peroxide-containing excipients are being made available, such as BASF's Kollidon 30 LP, to help address this issue.
- Particle size of fillers (for example, lactose, microcrystalline cellulose) is important depending on the formulation and manufacturing process.

What about a specific example – cellulose or PVP – how do you choose which is most suitable?

Most formulators favor specific excipients for particular types of formulation. For dry-granulation formulations, Kollidon VA64 has become the go to dry binder of choice for many because its properties are well suited to roller compaction processes (good compressibility and plasticity). However, in general the selection of functional excipients (binders and disintegrants) for a particular formulation should be based on the experimental evaluation of a range of candidates.

In the selection of excipients, it is also important to consider potential interactions with charged drug substances. Such interactions can result in incomplete recovery of the drug from the formulation, which can lead to assay irregularities or, worse, reduce the bioavailability of the drug. Non-ionic binders and disintegrants (for example, L-HPC, crospovidone) are less likely to interact with these types of drugs.

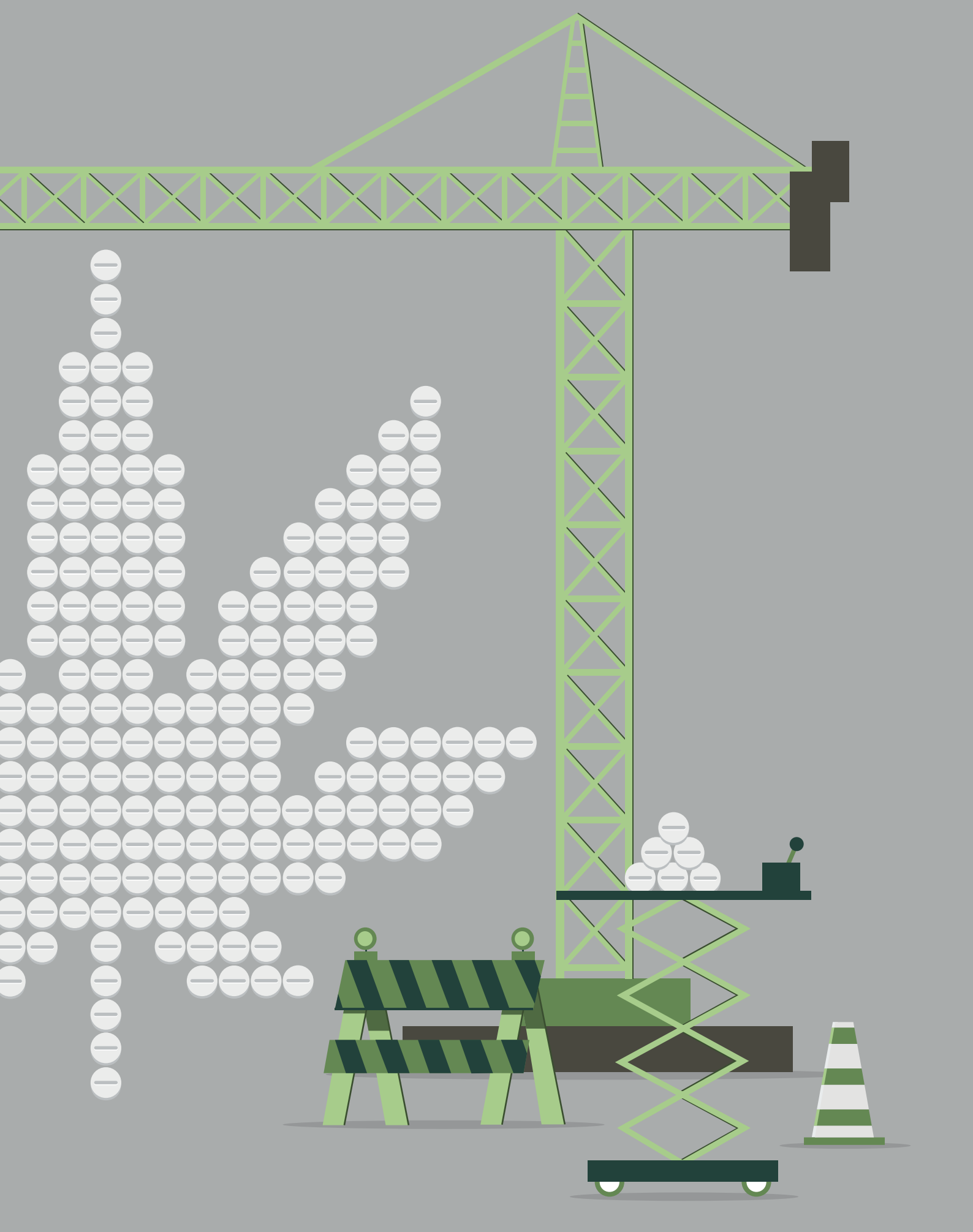
Where is there further room for improvement in the excipient field?

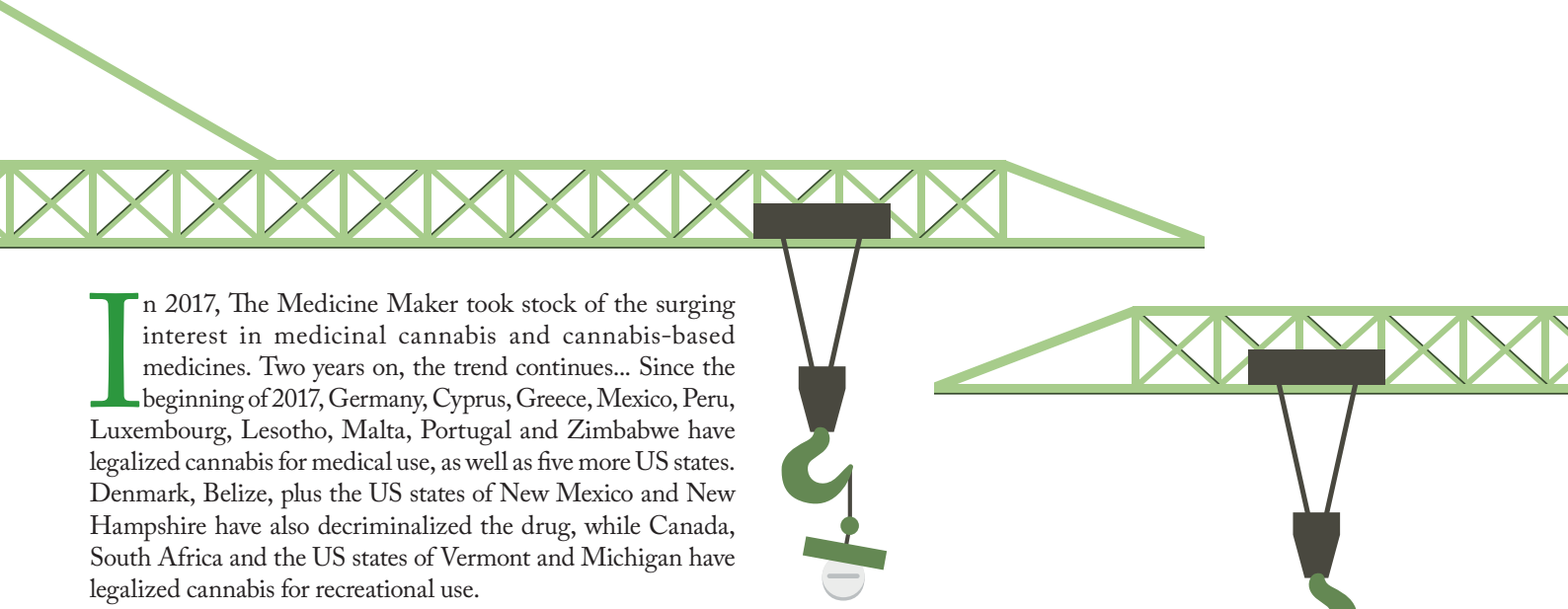
Solubility enhancement is one of the main issues facing formulators right now, but the tool kit of available, acceptable excipients has grown substantially in recent years; however, there continues to be a need for new excipients that can help overcome the challenges presented by difficult compounds.

UNDER CONSTRUCTION: PHARMA'S CANNABINOID BID

The cannabis business is booming as century-old legal conventions restricting use begin to unravel. Can pharma ride the wave with cannabis-based medicines? And how will drugmakers entering the fray deal with the dosage, delivery and bioavailability challenges?

By James Strachan





In 2017, The Medicine Maker took stock of the surging interest in medicinal cannabis and cannabis-based medicines. Two years on, the trend continues... Since the beginning of 2017, Germany, Cyprus, Greece, Mexico, Peru, Luxembourg, Lesotho, Malta, Portugal and Zimbabwe have legalized cannabis for medical use, as well as five more US states. Denmark, Belize, plus the US states of New Mexico and New Hampshire have also decriminalized the drug, while Canada, South Africa and the US states of Vermont and Michigan have legalized cannabis for recreational use.

With recreational cannabis legal in 10 US states and medical cannabis legal in 32 states, cannabis has become big business. One study found that, in the US, manufacturers and distributors, on both the recreational and medicinal sides, created 64,389 new jobs in 2018 – making it the fastest-growing labor market in the US (1). Sales of recreational cannabis are expected to grow 18.4 percent yearly, from $3.2 billion in 2018 to $12.5 billion in 2025, while sales of medical cannabis are expected to grow 11.8 percent per year from $5.1 billion in 2017 to an estimated $12.5 billion in 2025 (2).

But what about cannabis-based medicines? With medicinal cannabis becoming more widely accepted, will an increasing number of pharma companies seek to explore the therapeutic potential of the plant? Or does the "medical" or "medicinal" label only create confusion (and competition) for companies whose products are held to much higher standards of evidence by pharmaceutical regulators?

The FDA approval of GW Pharmaceuticals' Epidiolex was seen as a watershed moment for the industry, potentially ushering in a new era of cannabinoid medicines. Indeed, a number of companies are now addressing the manufacturing challenges of working with the cannabis plant to create safe and effective cannabis-based pharmaceutical drugs: is extraction or chemical synthesis the way to go? What about bioavailability? What about regulatory hurdles?

IS SYNTHETIC THE REAL DEAL?

A handful of cannabis-based medicines have already received regulatory approval, namely Sativex, Epidiolex (both from GW Pharma) and Dronabinol (marketed as Marinol and Syndros). The active ingredient in Epidiolex is cannabidiol (CBD), which is extracted and purified via crystallization from the cannabis plant, whereas Dronabinol is synthetic delta-9-tetrahydrocannabinol (THC). There is some debate as to which route holds most promise for the cannabis-based medicines industry.

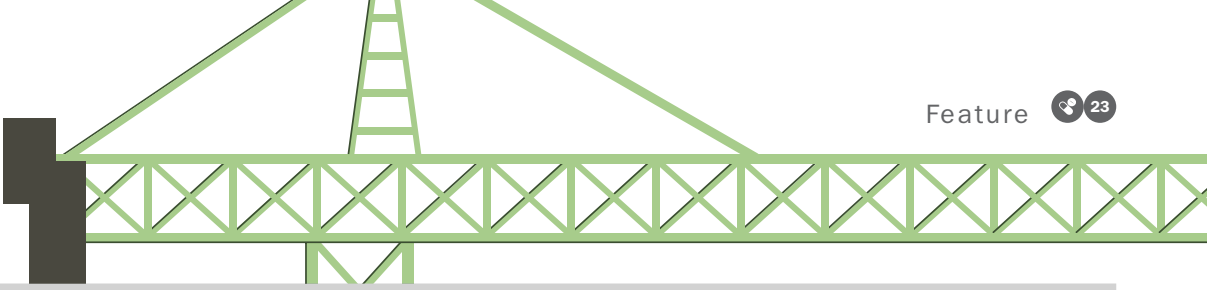
"GW has developed extensive expertise in the growing, extraction, and manufacture of cannabinoids for use within these medicines," says Chris Tovey, Chief Operating Officer at GW Pharmaceuticals. "We believe this tried and tested approach, honed over 20 years, allows us to develop a safe, consistent, and standardized product that patients and clinicians require/demand."

Tovey believes that plant-based cultivation is not more costly nor less efficient than synthetic production. "There are a number of different aspects to synthetic manufacturing that can make it a very costly process; for example, extensive equipment and chemical processes where maintenance and clean-up to remove toxic by-products can be difficult and expensive," says Tovey. "It is not uncommon for a medicine to be derived from plant-based material due to the inherent biological advantage in the synthesis of specific chemical isomers."

Johnson Matthey, which has over 15 years of developing and commercializing cannabinoids, focuses on the synthetic route for its cannabinoids, such as THC and cannabidiol. "Synthetic routes reduce problems with yield and impurity that arise through botanical extraction," says Kevin Hennessy, Global Director, New Business Development at Johnson Matthey. "Methods that rely on botanical extraction could have a high-degree of variability because of crop-to-crop differences." Synthetic routes may also provide for more reliable regulatory compliance, especially where GMP manufacturing is required. "There are no issues with raw material traceability and compliance, whereas farms could be resistant to GMP audits and issues with regulatory bodies," he adds.

Alyn McNaughton, Technical Director for Lonza Pharma, Biotech & Nutrition at its Edinburgh site points out that synthetic cannabinoids do have an advantage over plant-derived products because most plant-derived cannabinoids are classified as controlled substances unless they can be purified to a point where the psychoactive components are below the threshold at which they would be considered controlled (which can create some additional legal hurdles).

But Andrew Badrot, CEO of C^2 Pharma, which manufactures and distributes APIs extracted from plants, including cannabis, objects to the idea that synthetic APIs and naturally extracted



THE CANNABIS TRAILBLAZERS

A short introduction to GW Pharma, the company behind the world's first approved cannabis-based medicine.

By Chris Tovey, Chief Operating Officer, GW Pharmaceuticals

GW Pharmaceuticals is a UK-based company born in the late nineties – a time when similar conversations to those we have today – about the potential medical benefits of the cannabis plants – were taking place. Indeed, just as in 2017, patients marched on parliament to demand access to cannabis for medical purposes.

In 1998, the House of Lords Science and Technology Committee delivered a report on cannabis and cannabinoids. They concluded that, although cannabis and its derivatives should "continue to be controlled drugs" due to their potential harms, "clinical trials of cannabis for the treatment of MS and chronic pain should be mounted as a matter of urgency" (1). The message was clear: go forth and seriously study the potential therapeutic benefits of the plant through the usual scientific channels and create a bonafide medicine. And that was the challenge that Geoffrey Guy – who remains chairman – embraced, working alongside Brian Whittle, to found GW Pharmaceuticals that year.

Together, they set out to properly investigate the cannabis plant and the 100-plus cannabinoids contained within. They were originally based in Kent Science Park, where the company still maintains a strong presence. For the first 5-10 years, the focus was on research and development, but that work eventually led to the world's first cannabis-based pharmaceutical medicine: Sativex, a cannabis extract administered as a mouth spray, for the treatment of multiple sclerosis – thus directly responding to the original challenge set by the Lords committee.

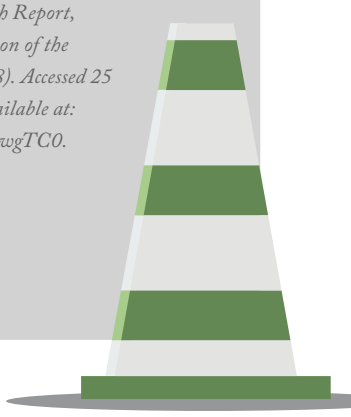
Sativex, originally approved in the UK in 2010, is now approved in over 25 countries. It is 50/50 CBD and THC, and is a natural plant-based material. Subsequent work focused on a cannabidiol oral solution, Epidiolex; and, in 2015, we initiated Phase III clinical trials for treatment of two orphan conditions in children – Dravet and Lennox-Gastaut syndromes. GW also received fast track designation from the FDA to treat children with epilepsy, which was given FDA approval in June 2018. This was a key milestone for the cannabis medicines industry – the first cannabis-based medicine approved in the US. Sativex isn't yet approved in the US, but we're hopeful that will change in the next couple of years. And we're also hopeful of an EU approval of Epidiolex in the coming months, which would be the first centrally approved cannabis medicine in Europe. We're also looking at additional indications, such as tubular sclerosis (TSC), where we have a pivotal study coming out soon.

The first 10 years or so of research was really the groundwork for our exploration of new therapeutic areas. We see promise in other areas of neurology, oncology and psychiatry, including autism spectrum disorder. Today, we have nearly 6000 patients involved in our clinical trials around the world, we've published 80 articles in peer-reviewed journals and we have generated 80,000 years' worth of safety data.

GW obviously generates a lot of interest because of the plant we're working on. But I'd like to point out that first and foremost, we are a pharmaceutical company trying to develop medicines that will make a difference to patient lives. It just so happens that we work with the cannabis plant. We believe passionately in the potential of the cannabis plant and that the best way to unlock that potential is to subject it to traditional pharmaceutical scrutiny so that we can ensure that the highest standards of safety, quality and efficacy are met.

Reference

1. *Select Committee on Science and Technology Ninth Report, "Chapter 8 opinion of the committee" (1998). Accessed 25 April, 2019. Available at: https://bit.ly/2PwgTC0.*



APIs are "different." He says, "So long as we are talking about the pure compounds and not an 'extract,' which may contain a combination of hundreds of different compounds, from a chemical standpoint, there is no difference. The molecule is the molecule." Badrot believes the only difference for API manufacturers is the starting material and the work up methods and purification of the compound versus having to produce it synthetically. "There are different costs and considerations associated with the manufacturing methods employed for synthetic versus naturally extracted APIs," he explains.

Badrot argues that for pharmaceutical companies, the difference will be with the impurity profiles of the API obtained naturally versus synthetically, given the different processes through which they are obtained. "The synthetic API will typically be 'cleaner' and only contain the target cannabinoid; therefore, especially for pharmaceutical indications, the plant extract will need to be purified in such a way that the level of 'immaterial' cannabinoids left in the extract are below the limit of 0.2 percent," he says.

"WHETHER EXTRACTING AND PURIFYING OR CHEMICALLY SYNTHESIZING CANNABIS COMPOUNDS, THERE ARE A NUMBER OF MANUFACTURING CHALLENGES FACING COMPANIES."

MAKING THE MEDICINE

Whether extracting and purifying or chemically synthesizing cannabis compounds, there are a number of manufacturing challenges facing companies. For C^2 Pharma, the challenges aren't at the API level, but rather those around regulations and how to grow and manage cannabis crops. "Hemp can be grown as a crop in certain locations, but with limitations regarding concentrations of THC in the plant," says Badrot. "We are still facing a very fluid landscape, and governmental organizations

CANNABIS COMPRESSED

Natoli Engineering has over 45 years of experience in tablet compression tooling and has been actively working in the cannabis space for over five years. Here, we speak with Jon Gaik, Stephen Natoli, and Randy Jung about the unique tableting challenges presented by cannabis-based products.

WHAT ARE THE MAIN CHALLENGES OF MANUFACTURING FORMULATIONS THAT USE CANNABIS OR CANNABINOID-BASED APIS?

The largest challenge when working with cannabis/cannabinoid-based APIs is the viscosity of the product. We are often approached by our cannabis customers to evaluate their processes and to provide assistance in troubleshooting their formulation as a result of inconsistent tablets or difficulty during tablet compression. We are able to use our experience in working with many "difficult" product formulations to offer assistance to solve cannabis tableting challenges that occur as a result of the formulation. Although the API is the most significant challenge, we have also helped customers solve other "common" tableting issues. Other challenges with cannabis tableting include: punch binding, tooling damage, high tablet ejection forces, inconsistent products, poor product quality, or failed third-party testing. We also have customers who encounter difficulties during tableting because of how they are processing or blending the different ingredients and API before tableting. Improper methods of processing the formulation can result in manufacturing issues during production on the tablet press. These difficulties include poor powder flow that results in inconsistent tablet weights, tablets not achieving the desired hardness, and material adhering to punch tips or collecting in the die walls. These circumstances often result in wasted API, loss of time, and missed production deadlines.

WHAT ARE THE BIGGEST DIFFERENCES COMPARED WITH CONVENTIONAL APIS AND FORMULATIONS?

In typical OSD (oral solid dosage) pharmaceutical or nutraceutical products, the API is a solid powder at room temperature. A primary difference for both THC and CBD is that the product often comes in a semi-solid oil and this semi-solid must be loaded into a carrier before being compressed into a tablet.

The target product profile for a typical cannabis tablet can be separated into three categories: efficacy/release, processability, and consumer preferences. Efficacy/release refers to how much API is needed and when is it delivered, such as a 5 mg immediate release tablet. Processability is largely determined by the excipients that are used to help overcome deficiencies in the tableting of the API – this could include binders that are used to enhance compaction or lubricants to assist with tablet release from the compression tooling. Other excipients may be added to the formulation based on consumer preferences; flavors and flavor enhancers are used for taste-masking and coloring can be used for branding or customer attraction.

CAN YOU EXPLAIN HOW THE "OIL-TO-POWDER" PROCESS WORKS?

The oil-to-powder process is required to make a viable tablet. One process occurs by heating the THC distillate (oil) to a specific temperature then adding the distillate to an API carrier excipient powder. This is then mixed using a standard induction mixer or, in some instances, a high-shear mixer. As mentioned above, a critical parameter is the ratio of the oil to the carrier excipient, as this dictates the processability and release nature of the product. Once the oil is loaded into the carrier, additional blending with other excipients, such as binders and taste masking excipients, may be needed to fulfill the target product profile.

HOW CAN COMPANIES ENSURE THAT THEIR CANNABIS FORMULATIONS WILL "PLAY NICELY" DURING MANUFACTURE?

The most important step is to characterize the formulation and understand the manufacturing scale-up process. Characterizing a formulation is accomplished by using a single-station press or an R&D rotary tablet press in single tablet mode to examine the compressibility of each ingredient separately. Evaluating the compressibility of the ingredients and determining how they compress when they combine is known as characterization processing.

Once the characterization process is complete, the next step is to make a small batch of test tablets on a rotary tablet press. Understanding various troubleshooting techniques will play a pivotal role during batch testing. For example, product sticking to the tooling or within the identifier (letters, numbers, logos, etc.) on the tooling may be the result of poor tablet design. Other issues that may occur are likely a result of powder flow in the hopper, die fill that controls tablet weight constancy, or heat build-up. Having a tablet press that is designed to reduce product flow issues and is equipped with turret and punch lubrication as well as an automatic cam greaser is going to be best-suited press for cannabis tablet production.

Jon Gaik is Director of Natoli Scientific, Stephen Natoli is International Technical Training Manager, and Randy Jung is Global Tablet Press Sales Manager, all at Natoli Engineering Company.

are not in-sync with each other. As the industry matures, and organizations see the broad range of potential, we believe all those things will be ironed out."

Another key problem that manufacturers face is removing unwanted cannabinoids during the extraction of APIs. "THC presents a real challenge for purification because it is naturally a non-crystalline oil. Impurities are chemically closely related, and prone to thermal and oxidative degradation," says Hennessy. "Purity is critically important as even trace amounts of THC are discouraged by our customers and regulatory bodies." Johnson Matthey invested early in large scale super-critical fluid chromatography (SFC), which Hennessy says works well for water insoluble lipophilic compounds, such as THC.

McNaughton agrees with Badrot that the major challenge in manufacturing synthetic cannabinoids is not necessarily in the chemistry. He sees three main challenges facing cannabis-based medicine manufacturing. The first is in handling and the regulatory aspects. "The non-psychoactive cannabinoids do not always fall under controlled substances regulation, but for those products that still retain their controlled drugs status, the strict controls around handling and transport means that development activities are extra challenging," he says.

Tovey agrees. GW's growing facilities and protocols, therefore, require highly stringent logistical and regulatory controls. "We are inspected by health regulators like the UK MHRA and the US FDA, and require further inspection and a special license from the UK Home Office to operate," says Tovey. Much like all medicines, cannabis-based medicines are in accordance with "Good x Practices" (GxPs) during their development, which continue beyond regulatory approval and throughout the lifecycle of a medicine. "For us, these include Good Manufacturing Practice (GMP) and Good Agricultural Collection Practices (GACP)," says Tovey. "These GxPs are policed and enforced by statutory bodies with the legal powers to revoke licenses when not followed or adhered to."

Tovey notes that achieving batch-to-batch consistency for plant-

"MANY CANNABINOIDS ARE LIPOPHILIC AND EVEN IN THEIR PUREST FORMS ARE EITHER OILS OR OILY SOLIDS, RATHER THAN THE WHITE POWDERS SO COMMONLY SEEN WITH MORE TYPICAL PHARMACEUTICAL APIS."

derived drugs shouldn't be underestimated. "Due to the differences in cannabis starting materials and methods of manufacture used to prepare cannabinoid/cannabis-based medicines, the chemical profile of the extracts and finished products have the potential to vary enormously – both in terms of the presence of desired components (cannabinoid profile) and undesired components (impurities, degradants and potential adulterants [fungal or bacterial contaminants, pesticides, heavy metals, and so on])," says Tovey.

Cannabinoids are present in the cannabis plant as acids and are inherently unstable in this form at room temperature. According to Tovey, the instability means that it is important to control the extraction and other processes within the manufacturing method (for example, decarboxylation) carefully, as these can affect the content and stability of the resulting extract or product. "It can be challenging to control all of these parameters to maintain batch-to-batch consistency and stability. Achieving a highly bioavailable, convenient, stable dosage form of an appropriate size to allow appropriate titration is therefore a significant challenge when it comes to cannabis-based medicines or cannabinoid/cannabis-based products," Tovey explains.

McNaughton echoes the same problems – especially bioavailability – as a second challenge. Many cannabinoids are lipophilic and even in their purest forms are either oils or oily solids, rather than the white powders so commonly seen with more typical pharmaceutical APIs. And that poses challenges for dosage, delivery and bioavailability. "Most cannabinoids suffer from first-pass metabolism and are broken down in the liver before they reach general circulation," says McNaughton. "Consequently, the oral bioavailability of cannabinoids is generally in the region of four to 20 percent, resulting in most of the material swallowed having no effect on the body. Lipidic formulation enables the transformation of oily material into an emulsion that is miscible with water and, therefore, better absorbed by the body. In addition, because these materials are so greasy and have such a high affinity for oils, lipids can also be used to promote lymphatic absorption, which bypasses liver degradation but still delivers the drug substance to the bloodstream."

Tovey adds, "For complex plant-based extracts (such as cannabis extracts), the presence of other non-cannabinoid, typical

"EVEN IN COUNTRIES, SUCH AS CANADA, WHICH HAVE ALREADY DECRIMINALIZED CANNABIS, THERE IS STILL VARIATION IN THE INDIVIDUAL PROVINCE OR TERRITORY LEGISLATION."

plant-based components, such as waxes, flavonoids, terpenes, sesquiterpenes and so on, all add to the complexity and solubility issues when trying to find an appropriate formulation."

Finally, according to McNaughton, the dosage form also needs to be adapted to the oily liquid nature of these formulations. "Liquid filled hard capsules and soft gel capsules are ideally suited for this family of medicines," he says.

MEDICINAL, MEDICAL AND RECREATIONAL

Following the legalization of cannabis in Canada, South Africa and several US-states, a big question for pharmaceutical companies in this space is whether debates around legalization and scheduling would make it easier to develop and manufacture cannabis-based medicines. C^2 Pharma sees its business as being totally separate from debates around legalization. "We are talking about two different things," says Badrot. "If you take caffeine as an example, it is applied in both social and pharmaceutical markets, and each one can create their own value stream. Like caffeine, the cannabis market has plenty of space to thrive, but our interest remains on the pharmaceutical side."

Lonza, on the other hand, has found that differences in legislation can create some logistical problems. "The controlled drugs laws are a large complication in the development of cannabinoids; firstly, as there is a lot of variation in these laws from country to country or even state to state, such as in the US," says McNaughton. "Even in countries, such as Canada, which have already decriminalized cannabis, there is still variation in the individual province or territory legislation. Transporting products to legal zones without impacting areas where it remains illegal is a logistical challenge."

GW Pharma has been asked a lot over the last couple of years whether the legalization of cannabis would make their lives easier. The answer, according to Tovey, is that it wouldn't make a big difference. "Ultimately, because we have chosen to go down the traditional pharmaceutical path, we're almost entirely removed from the debate around legalization and even scheduling, to a certain extent," he says. "We've never had a notable issue in getting the licenses to grow and research cannabis, to do all of

the clinical trials and to turn it into a medicine and get regulatory approval." Although Tovey does admit that there were some challenges. "It required a lot of expertise, time and attention to detail. And you have to constantly ensure that you've got your licenses up to date. But we have shown that it is possible to do all of this work within a system in which cannabis isn't legalized, and even where cannabis was schedule one."

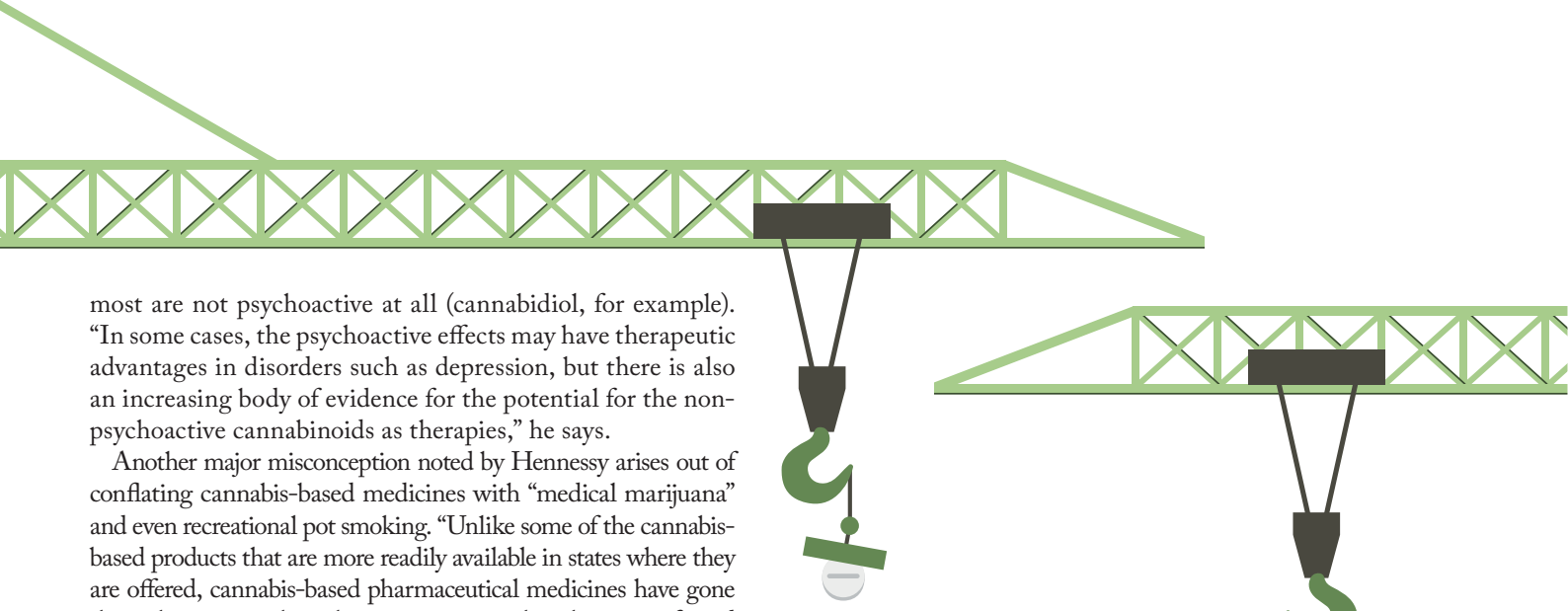
Tovey has many good things to say about the environment in the UK for manufacturing and developing cannabis-based medicines – despite the legal status of the plant. "The UK government and regulators have always been supportive in the way they approach things, and we've found the UK to be a conducive and attractive environment for growing and manufacturing cannabis and cannabis-based medicines." He believes that his experience is similar to that of other companies in the UK that hold licenses for growing cannabis and undertaking cannabinoid research. "The UK should be proud that the country is a world leader in cannabinoid research, partly through GW's work, but also through the extensive network of academics we work with."

COMBATING CONFUSION AND CONFLATION

Despite GW's success in the field, there are some misconceptions that pharma companies face.

"We are looking at products derived from a plant that has substantial social implications. Some people believe that anything related to the plant is to be avoided, while others may believe that cannabis-derived compounds will heal everything from your head to your toes," says Badrot. "What we are looking to do is to create a realistic balance between realizing the potential of cannabis and its constituents, and delivering patient solutions that work. Over the next decade, we expect to see a lot of progress in the space and are excited to be one of the trailblazers in the market."

For McNaughton, a major misconception is that all cannabinoids are psychoactive, which isn't the case. In fact,



most are not psychoactive at all (cannabidiol, for example). "In some cases, the psychoactive effects may have therapeutic advantages in disorders such as depression, but there is also an increasing body of evidence for the potential for the non-psychoactive cannabinoids as therapies," he says.

Another major misconception noted by Hennessy arises out of conflating cannabis-based medicines with "medical marijuana" and even recreational pot smoking. "Unlike some of the cannabis-based products that are more readily available in states where they are offered, cannabis-based pharmaceutical medicines have gone through rigorous clinical testing to prove that they are safe and effective," says Hennessy.

"Unfortunately, the science around the active compounds of cannabis – CBD and THC mainly – is still nascent, and even more so when you consider interactions between the two," Badrot adds. "Legally, the term 'medical cannabis' is open to interpretation."

Within the cannabis space, there is a broad array of different products that are commonly referred to as medicinal cannabis or medical cannabis. Tovey says, "That might include some of the finished products you see being sold in the US or Canada, but it could include some of the CBD products on the shelves, or even people smoking a joint for purported medical reasons. This whole category of products vary greatly in their safety, quality and efficacy, but none have been subjected to double-blind placebo controlled trials – what the pharmaceutical industry would consider hard evidence." He also adds that the term "medical cannabis" is sometimes deliberately conflated with cannabis-based medicines. "There isn't a strong evidence base for those products and we cannot extrapolate from data generated by cannabis-based medicines to a whole group of products," he says.

In a Q&A note, the FDA has stated it "continues to be concerned at the proliferation of products asserting to contain CBD that are marketed for therapeutic or medical uses although they have not been approved by FDA [...] Unlike drugs approved by FDA, products that have not been subject to FDA review as part of the drug approval process have not been evaluated as to whether they work, what the proper dosage may be if they do work, how they could interact with other drugs, or whether they have dangerous side effects or other safety concerns" (3).

Tovey points out that the evidence for GW's cannabidiol oral solution should not be extrapolated to other cannabidiol containing product formulations. "Each product needs to be assessed on its own merit through thorough pre-clinical and clinical evaluation. The safety and efficacy demonstrated in pre-clinical and clinical trials of approved or late-stage investigational medicines does not equate to the same efficacy or safety profile in different products of similar or the same cannabinoid composition – doing so assumes different products have been grown and manufactured to exactly the same standards."

There is also a common misconception that randomized clinical trials cannot be conducted with cannabis derived medicines, according to Tovey. "With Epidiolex and Sativex, we have shown that this is not the case." The current lack of randomized controlled trials performed with cannabinoid/cannabis-based products, says Tovey, is due to the lack of quality investigational products. "This is as a result of the challenges around the ability to manufacture and supply a consistent, stable product which can be reproduced throughout a medicine's development and life cycle after market authorization."

Despite this, Badrot believes that the medical cannabis industry is breaking down stigmas, which can only encourage more companies to enter the cannabis-based medicines industry. "The stigma that has been created since the 1920s and the initial ban of 'Indian hemp' during the International Opium Convention is starting to loosen, particularly in a time where we see a critical gap in the pain medication market and the crippling effects of the opioid epidemic. Cannabis offers great potential for safe, effective solutions," he says. "Cannabis is effective, but it is also misunderstood."

As public interest grows in the space, Badrot believes more pharmaceutical companies are willing to explore the opportunities that cannabis presents. "We are just starting to explore what the full potential could be."

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Built on Innovation

Innovation in glass continues to be a key enabler for allowing pharma manufacturers to make better, safer products for patients. This has been SCHOTT's mantra for more than 130 years – why stop now?

SCHOTT's history dates back to 1879 when the company's founder, Otto Schott, invented a special lithium-based glass with novel optical properties and shared his discovery with Ernst Abbe. This laid the foundation for a close collaboration, which soon resulted in Otto Schott, Ernst Abbe, Carl and Roderich Zeiss founding the Schott & Associates Glass Technology Laboratory in Jena, Germany, in 1884 (today's SCHOTT AG). The company also invented chemically resistant borosilicate glass, which has since become the main primary packaging material for use in pharma packaging. SCHOTT's history is built on enabling customers to develop high-performance products and the company continues to innovate today. SCHOTT produces 11 billion pharmaceutical containers every year and is also one of the few companies that is in control of its entire value chain – something that is becoming more and more important to pharma customers. Companies no longer just want a container; they expect services to come with it too, such as leachables profiles, extractables profiles and regulatory support.

We speak with Dr Frank Heinricht, Chairman of the Management Board of SCHOTT AG, to talk about the company's recent $1 billion investment in its pharma glass business, industry trends and the importance of glass innovation.

Tell us about the company's $1 billion investment…

As the overall pharma market grows – and particularly with new drugs such as biologics growing at an above average rate – there is a risk of shortages in quality pharmaceutical glass. We are investing $1 billion globally in our pharmaceutical packaging business through 2025 to shore up our capacity. The investment will be used for a number of different projects, including a glass tubing production facility in China and additional tanks and infrastructure in India, where we are seeing increasing demand. Particularly in India, there is huge growth as drug production is transferred from Europe and the US.

Other projects for the investment include a new glass syringe operation in Switzerland, and a new factory in the south of Germany (Müllheim) for SCHOTT TOPPAC ready-to-use polymer syringes and customized container solutions. Overall, our capacity for polymer packaging will be expanded by 50 percent by 2020, and an additional 50 percent over the coming years. We'll also be expanding our high-value vial production line, including a boost for our

new EVERIC pure vials and investment in our iQ platform of ready-to-use vials. Several investments will be completed by the end of 2019.

Why is innovation in glass so important?

My background lies in physics and I'm passionate about innovation – and for a materials-based company like SCHOTT, it is imperative that innovation is the driving force of what we do. Our designs

must be led by science and the science of glass is more fascinating than most people realize. Glass is not all the same – a lot of effort goes into making the right glass for use in pharmaceuticals. For example, the bottom-near heel region of standard vials often acquires an inhomogeneous chemical structure during the forming process and is prone to ion exchange, which may potentially harm the drug. Physics and chemistry dictate that there will always be some kind of interference between the drug and the glass, and there is an art to designing the right container made out of borosilicate glass that really minimizes this interference – getting it as close to zero as possible. We have developed different coatings and different glass treatments to ensure that we can offer a very specific solution for every API, ensuring that products have a long shelf life with no risk to the patient.

We want to give our customers options. Not everyone follows the same path forward so it's important for suppliers like us to have a huge toolbox that allows customers to select the right product to suit their needs – perhaps a ready-to-use container that has been made in the right way with the right raw materials, or a container with a specific strength, for example. Right now, requirements are becoming tighter and tighter when it comes to particles and there is also a growing demand for traceability in the supply chain – customers want to know the history of a container, including how it was made, when it was made and so on. Traceability has always been very important to SCHOTT.

What other trends are you seeing in the pharma market?

Although quality expectations are already high in the pharma industry, the bar is being raised even further. The FDA is constantly pushing manufacturers to provide better medicines. With particulates, for example, the standard limit a few years ago was around 300 microns. Today, it's closer to 100 microns. Regulators in other countries are also looking to follow FDA standards when overhauling their own pharma regulations.

In addition, drugs are becoming more sensitive and specialized. There are over 3000 drugs in the pipeline and roughly two thirds of these are biopharmaceuticals. These sensitive drugs have specific requirements in terms of packaging – and this is why we have launched products recently that specifically cater to sensitive drugs. There is also a lot of focus on cell and gene therapy and personalized medicines. Many new drugs will target smaller patient populations, so low-fill operations and flexible manufacturing will be significant trends for the foreseeable future.

What are some of the latest innovations from SCHOTT?

SyriQ BioPure was launched in 2018 and has had a positive reaction from customers. With the newest innovation of our syriQ BioPure range, we were the first company to introduce a syringe that uses no lubricant. It was specifically designed with the sensitive needs of biologics in mind. The interaction between silicone and biologic drugs has been a concern in industry, but being silicone free eliminates that problem.

In 2019, we launched EVERIC, which is something I am very excited about. EVERIC has been designed as a modular concept. It provides customers with a unique combination of attributes to package biologic drugs – they can pick what they need; for example, they may choose to prioritize strength, machinability or an order of magnitude improved extractables and leachables profile. As I mentioned earlier, it is important to give customers options so that there is always something that suits their products and processes. With EVERIC, customers can use the material they already know and have registered, namely FIOLAX® CHR borosilicate glass, and then select the additional features they would like to add to improve the performance of the product. Cost is always an issue for pharmaceutical companies so with a modular approach they can select the performance they really need, balanced with their budget. There are three main modular elements: Pure, Strong, and Smooth. EVERIC Pure, which is available now, is all about the interaction with the drug and container, and is suitable for sensitive drugs with low filling volumes. It ensures drug stability by using an improved Borosilicate glass tubing. The other modules are currently in testing. EVERIC strong emphasizes strength and preventing breakage by optimizing the geometry through mathematical simulation. EVERIC smooth is designed to give improved container flow through conventional bulk filling lines thanks to a coating on the outer surface. To ensure that unimpeded visual inspection can still take place, the surface treatment is abrasion-free, fully transparent and limited to the most relevant areas of the vial, such as the sidewall. We can therefore improve the coefficient of friction (COF) by 80 percent.

How do you ensure your new innovations are easy for pharma companies to adopt?

EVERIC is based on the gold standard in the pharmaceutical packaging industry, namely borosilicate glass. Depending on your chosen options you can better control delamination, or have an improved E&L profile, but ultimately it is the same glass. With any of our innovations, we collect a lot of data and use this to steer our design process, and we also work with the FDA on pre-registration to make it easier for our customers to go through the regulatory processes.

SCHOTT's role is to always support the pharmaceutical industry as much as possible. Our $1 billion investment is all about enhancing our capability to support the industry. Our slogan is, "Innovators at heart and enablers at work." Our role is to innovate to help our customers come up with better products for patients.

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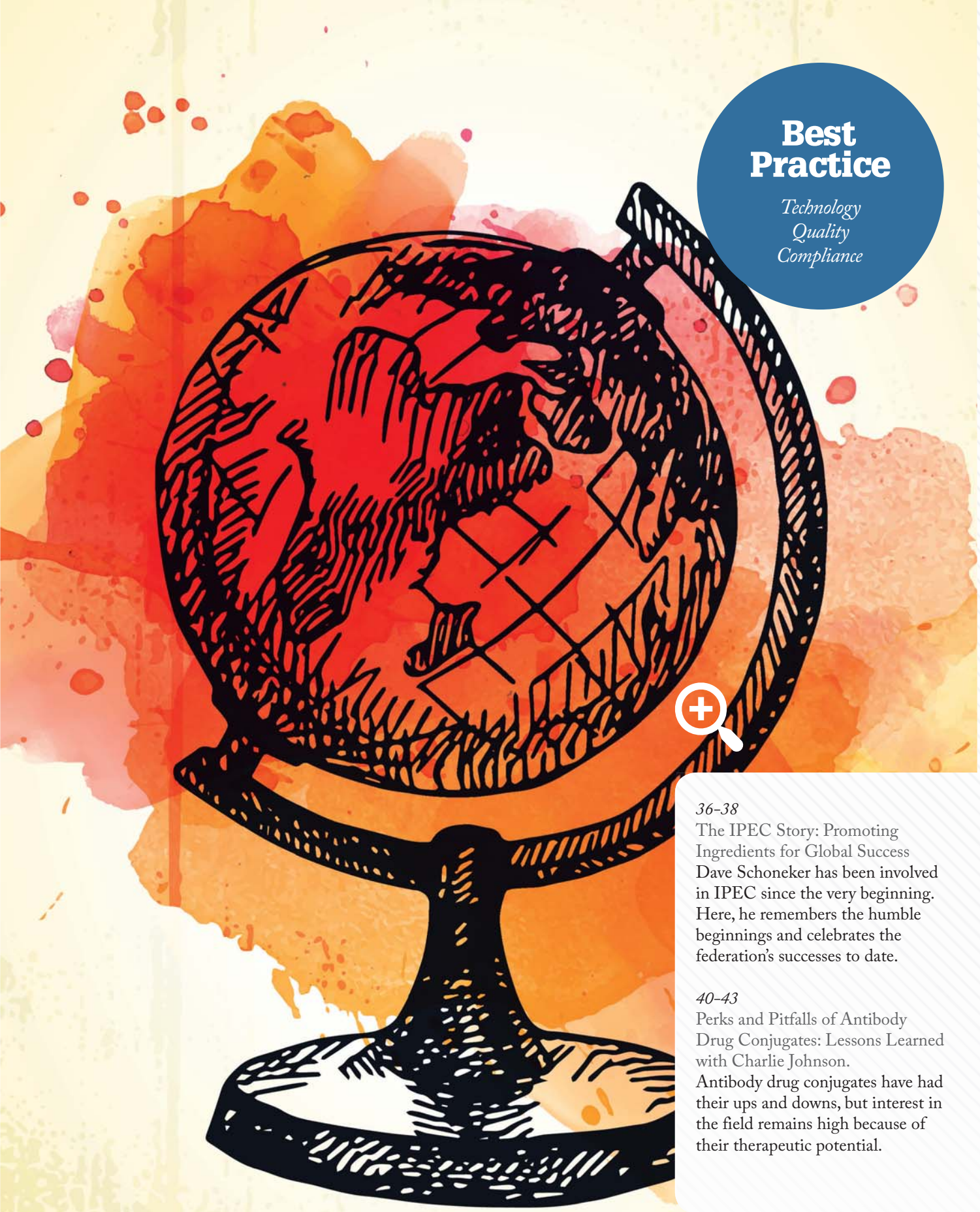

The IPEC Story: Promoting Ingredients for Global Success

High quality excipients make all the difference to the drug development process. And yet, for years, excipients were often overlooked by the industry. Today, IPEC is helping to give excipients the recognition they deserve.

With David Schoneker

My mentor – and now departed friend – Lou Blecher used to say, "Excipients don't get any respect." He was right. For many years, excipients were the second-class components of drug development. It's understandable why the API steals all the glory. The API is what gives a medicine its therapeutic properties, but without excipients we wouldn't be able to deliver medicines effectively to patients. The right choice of excipients can enable companies to more readily manufacture their drug product, produce a stable dosage form, improve shelf life, help with swallowability, enhance patient safety in terms of compliance, and more. Excipients make up a huge percentage of an actual tablet – in some cases up to 99.9 percent!

Today, more and more people in the industry understand and respect the role that excipients play. And I think a lot of this comes down to the work that the International Pharmaceutical Excipient Council (IPEC) has done. The IPEC Federation is a global organization that promotes quality in pharma excipients. I've been involved in IPEC since its inception in 1991 and, over the course of three decades, I've seen the benefit of the policies and guidelines that we have created for the industry. Many companies have grown to become top-quality industry suppliers that meet globally vetted standards thanks to the work of IPEC.

One of the biggest challenges with regulating pharmaceutical excipients is that most are made by chemical companies, who make materials for wider industrial use. As well as producing excipients for medicines, they will also be marketing these products to food companies, paint companies, plastics companies, and more. In fact, excipients for pharmaceutical use make up only a fraction of customers for the chemicals industry – and yet the pharma industry has specific GMP regulations for excipients because of the way in which they will be used.

When IPEC was first finding its feet, the unique challenges of the industry were

not being addressed with the same level of scrutiny that was given to the production of finished pharmaceutical products or APIs. There was simply no clear GMP regulation in place for excipient operations and the lack of harmonization left many in a state of confusion about what specifications and controls the sector should be using. For example, it was quite normal for an excipient supplier to be told by one customer that its processes were exemplary, and completely unacceptable by another… a frustrating experience! Standards were being interpreted in different ways and arguments were hindering the industry. Some pharma companies wanted the standards at excipient plants to mirror their own but there are limits to what chemical companies are able, or indeed willing, to do when pharmaceuticals are such a small part of their business.

Wine, cheese, and humble beginnings

Many businesses have stories of humble beginnings. Apple, for example, began in a garage in California and when Starbucks first opened its doors in 1971, neither a coffee was brewed nor a pastry sold (the company sold coffee beans and roasting equipment). But when I tell people the story of the early days of IPEC, people chuckle in disbelief. Today, IPEC is an internationally recognized organization, with regional groups in the Americas, Europe, Japan, China and India. IPEC also has partnerships with other associations in Canada, Mexico, Brazil and Argentina. It has tremendous respect worldwide. But the organization's story began with a good wine and cheese party…

In the early 90s, as part of International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) initiatives, the US, European and Japanese pharmacopoeias were eager to harmonize their standards. In particular, they identified that specifications and test methods for excipients were, frankly, a bit all over the place! They felt it was a good area for them to start to work on harmonization and they outlined their thoughts at a conference in Orlando, Florida, which I attended.

Though these early intentions of the pharmacopoeias were noble, at that time they didn't have the scope and experience that we, whose careers revolved around excipients and formulation, had to truly understand what was needed. After the first day of the conference, Lou Blecher, invited me and others to his hotel room to discuss what we had heard and what those of us in the industry could do to assist the pharmacopeias' efforts.

Around 18 chemists and formulators descended on Lou's room, and were invited to enjoy a spread of cheese and wine. As thoughts were thrown around (and wine poured), Lou proposed that we form a trade association. Unlike others, this association would be about science, not business, and the association would be for both the makers and the users of excipients. We decided that if we were meeting the needs of patients and working to ensure that the guidelines we produced helped harmonize the industry, then an increased market presence would naturally occur. The idea certainly sounded good at the time, but we all realized that the wine might be influencing our reasoning...

By the next morning, we still thought the idea was worth pursuing and could make a huge difference if we formed such an organization. We also acknowledged that, as scientists, we knew little about the legal processes required to bring this concept into reality. Fortunately, Lou was able to contact a friend (Bob Pinco), who was a lawyer that previously worked for the FDA, to help us formulate a legal framework for our new project. And within weeks we had our first organizational meeting.

Several companies were great supporters from the start, including my own employer, Colorcon; with a number of employees around the world involved in IPEC from the start! The company was certainly supportive of our cause to help harmonize standards for excipients. Other companies that also got involved in those early days were GAF (which later became ISP, then Ashland), Hercules, (now Ashland), Merck, Sharpe and Dohme, Dow Chemical (now Dupont), Hoffman La-Roche (now Roche) and Servier to name a few specifically.

During one of IPEC's early meetings, I suggested that, as well as working with the international pharmacopoeias to harmonize their standards, an effort should be made to help unify GMP standards for excipients. In my role as Director of Quality at Colorcon, I was having to deal with the issue of differing opinions from one customer to the next, and I wondered if others were also experiencing the same problems. From the perspectives of both the end-users and producers of excipients, the idea made sense for the industry and was welcomed by both sides. IPEC's GMP committee was set up soon after and was involved in the development and publication of the first excipient GMP guideline in 1995. Internationally recognized and used as the basis for most of the standards on excipients (to date), the publication was one of our first major accomplishments – and a powerful statement as to what the association could achieve.

IPEC has been going for almost 30 years now, and we've had some great successes and a huge impact on the international mindset toward excipients! Not bad for a group of scientists who crammed themselves into a tiny room late one evening for cheese, wine and a discussion about excipients!

Out with the old

IPEC has helped solve a number of issues for excipient and pharmaceutical companies and published a joint IPEC-PQG Good Manufacturing Practices Guide, a Good Distribution Practices Guide, an Excipient Qualification Guide, a Certificate of Analysis Guide, the Significant Change Guide for Pharmaceutical Excipients, a Technically Unavoidable Particle Profile Guide, and many more (all available at www.ipec.org). But there are still other challenges. One frustration is that although excipient companies are developing some

David Schoneker recently received the Louis Blecher Memorial Outstanding Lifetime Achievement award from IPEC.

truly innovative technologies, they are not being used by the industry due to a reluctance to be first. If new excipient products continue to be unused, then it could affect innovation in excipients going forward; after all, a lot of work and cost goes into creating a new excipient, including market research and regulatory work.

Ever since the formation of IPEC, the concern about bringing novel excipients to market has lingered – perhaps hardly surprising given the notoriously conservative and safety conscious attitude of the pharma industry. Historically, the industry has continued to formulate with 100-year-old excipients – and although these may work, they do not always work as well as they should. Pharmaceutical companies do acknowledge the benefits of new excipients, but they rarely want to be the first to use them. Companies can also be hesitant to use modified versions of well-known excipients in their drug products. I've seen excipients companies develop some advanced co-processed formulations of commonly used excipients, such as spray dried versions of corn starch and pregelatinized corn starch, that give better performance – pharma companies have even raved about the benefits! But still they dismiss them in preference of more established options that have precedence of use.

The reluctance of pharmaceutical companies to adopt new excipients may be tied to the fact that the FDA lacks robust regulation on the introduction of new excipients to market. Currently, there is no independent process for the FDA to review the safety of an excipient; excipients cannot be approved on their own and must be a part of a drug product and reviewed during the drug registration and approval. The only process available to pharma is to take the plunge and see what happens when a novel excipient is added to their formulation – a choice which many companies are simply unwilling to make.

The crux of the issue is that now, more than ever, pharmaceutical companies need new ideas to help develop drug formulations for their pipelines. There are more insoluble APIs than ever, thanks to new technologies and techniques, and new excipients may be needed to optimize formulations for emerging technologies, such as 3D printing and continuous manufacturing. Countless numbers of drugs sent to the FDA for approval have been scrapped because the right dosage forms required for the effective delivery of these products were not available – a terrible situation when we have so many innovative options in an industry that could help!

IPEC and the IQ Consortium (https://iqconsortium.org) have teamed up to hold discussions with the FDA to establish a novel excipient qualification process, which I really hope could result in the formation of an FDA committee to review data on new excipients. If the FDA agrees to this, it would go a long way in mitigating the industry's concerns and allow companies to jump in and use newer materials, which could resolve many issues they face in terms of drug development, stability and quality. The pharma industry is one of the most innovative industries in the world – and we can do better if companies are given the help they need to be confident in adopting new ingredients and technologies.

IPEC has, throughout its history, helped put a spotlight on excipients and worked with regulators to affect change. We haven't lost the enthusiasm or verve we had when we first created the association! I hope we will continue to make progress in this area. The risks of ignoring the problem are great. If companies continue to avoid novel excipients then it could lead to a stagnation in innovation – a problem for pharma and patients alike.

Dave Schoneker is Global Regulatory Director, Strategic Relationships at Colorcon, and Vice Chair for Science and Regulatory Policy for IPEC.

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Perks and Pitfalls of Antibody Drug Conjugates: Lessons Learned with Charlie Johnson

ADCs have suffered a few setbacks over the years, but interest in their therapeutic potential – particularly against cancer – remains high.

By Stephanie Sutton

Charlie Johnson has kept his eye on the antibody drug conjugate (ADC) field since its early days and was involved in developing the process for one of the first ADCs to hit the market, as well as helping to establish Avecia's ADC manufacturing operations. Today, he is CEO of ADC Bio. Here, he talks about the ups and downs of the ADC market, and shares the lessons he has learned as ADC Bio gears up to jump into GMP manufacturing.

New classes of therapeutics take time to find their feet

I've always been fascinated by ADCs. In many ways, ADCs combine the best of both worlds: the potency of cytotoxic agents with the specificity of antibodies. The targeting ability has been of particular interest to drug developers working on cancer therapeutics. But although the industry has been talking about ADCs for years, approvals have been thin on the ground. ADCs have shown promising data in terms of having an effect on tumor cells, but there have also been unintended side effects as the target antigen on the tumor may also be present in healthy tissue. The translational science of ADCs has been very challenging, but a lot of it comes down to choosing the right targets. Right now, there is a great deal of attention being paid to more exquisite targeting; for example, using bispecific ADCs.

It is normal for new areas of science and drug development to suffer some setbacks, but there is now a renaissance in the ADC area, thanks to growing understanding and experience with ADCs. Two new products were approved in 2017 and there are over 80 ADCs in clinical development, as well as thousands of patents filed. And new research is being published constantly as the community strives to improve safety and efficacy (for just some example papers

published in 2019, see the Recommended Reading sidebar). Oncology remains the top area for ADC drug development, but other areas are also being explored, such as inflammatory diseases and even bacterial infections.

Aggregation is a major manufacturing challenge

As well as innovation in terms of ADC development, improvements in manufacturing have focused on speeding up, simplifying and significantly lowering the production costs. My work with ADCs began back in 2005. I was working in Scotland at a clinical manufacturing facility for small molecules (mainly cytotoxics) and we received a visit from a small company that I had never heard of before: Seattle Genetics. They were developing what would later become Adcetris and we were involved in developing the process for them.

After I left the company, I kept my finger on the pulse with ADCs. The field certainly had its challenges, but I was not only fascinated by the way they worked and their therapeutic potential but also by the interest shown by companies. Around 2009, I had a conversation with an ex-colleague who had come across a piece of intriguing chemistry that he thought could help us towards a solid phase approach to ADC manufacture.

Currently available ADCs get around the aggregation issue with finely tuned processing, but many ADCs in development now use pyrrolobenzodiazepines or duocarmycin-based payloads, which are very potent but also dramatically increase the drug's propensity to aggregate during conjugation, which is expensive and time consuming to deal with. By using proprietary beads to immobilize the antibodies, payloads can be conjugated in situ, which physically prevents aggregation at the source. It also means you get a very high-purity ADC.

Pharma companies want you to do as much work for them as possible

Inspired by the technology, we worked to optimize it with the University of Sheffield. ADC Bio was formed in 2010. Our initial aim was to license the technology out to pharma companies. Though there was a lot of interest, there was also a common theme: companies wanted us to actually do the work for them.

So that's the direction we went in. We only focus on ADCs. Our proprietary technology is called Lock-Release, and we've done the work to ensure it's scalable and meets GMP requirements. But we also do mainstream ADC development too, including small-scale work that has gone into trials in non-human primates. We were a small company at first – we had nine people in 2014 but things changed quickly. We've expanded a lot and by 2015, we were turning over £1.5 million. We signed many agreements and even won an award with the British Private Equity and Venture Capital Association!

But still customers wanted more. Many clients were encouraging us to get further involved in their development programs; they wanted us to move into GMP manufacture and clinical trials. It was a big move. ADCs are still relatively new compared with established monoclonal antibodies, but after we discussed the expansion we were confident it would work. Between us we had a lot of experience in ADCs, so the question became: why not take the plunge?! The hardest part of making an ADC is the design and development, but GMP is where pharma customers see the most value as it's directly connected to the patient. In fact, GMP is relatively simple compared with other aspects of ADC development. Once a recipe has been defined, it's simply a case of following the recipe at scale – providing your process development is solid.

The decision was made – and we went to our investors and told them we wanted to build a clinical manufacturing facility. It took time, but we got the funding. We acquired a 6500 m^2 facility in Deeside, UK, in 2017. Construction has finished and we're awaiting inspections as we speak; we have been liaising with the MHRA

Recommended Reading

M Abdollahpour-Alitappeh et al., "Antibody–drug conjugates (ADCs) for cancer therapy: Strategies, challenges, and successes," Journal of Cellular Physiology, 5 (2019).

L Bourillon et al., "An auristatin-based antibody-drug conjugate targeting HER3 enhances the radiation response in pancreatic cancer," International Journal of Cancer (2019).

C Duerr, W Friess, "Antibody-drug conjugates- stability and formulation," European Journal of Pharmaceutics and Biopharmaceutics," 139, 168-176 (2019).

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M Lin Yap, "Activated platelets in the tumor microenvironment for targeting of antibody-drug conjugates to tumors and metastases," Theranostics, 4, 1154-1169 (2019).

M Jose Costa et al., "Optimal design, anti-tumour efficacy and tolerability of anti-CXCR4 antibody drug conjugates," Scientific Reports, 9 (2019).

throughout the design and construction process. We are now part way through the accreditation to obtaining the necessary license to produce ADCs for human trials.

Build flexibility into your facility design

Experts will tell you that the design and build of a new facility takes time – and they are absolutely correct! Flexibility is extremely important. While we were in the process of building our Deeside facility, there was a big shift in the ADC marketplace. There are four elements of manufacturing an ADC: you need an antibody, a payload, the conjugation, and then fill and finish. Not all pharma companies want to do this in house so outsourcing is a common option and, in some cases, each element will be manufactured at a different site. Today, however, companies tend to want their partner to tackle multiple aspects – perhaps make the antibody and do the conjugation with the payload, or do the conjugation and the fill and finish. The reason? Time. It saves the pharma company a lot of time in development. They can also save costs because they need fewer people and aren't dealing with complex work.

Having more than one part of your supply chain with one vendor also contractually makes things a lot simpler and gives you more flexibility to overlap the next stage of manufacture with completion of testing in the preceding stage. If you are transferring to another site then you must ensure the product is always to specification. But if you have formulation under the same roof, the client can ask you to try different approaches with the idea of compressing time or investigating ways to make processes more efficient.

As well as performing ADC manufacturing and conjugation, we are also moving into fill and finish. Fortunately for us, we prioritized flexibility when looking for a site so we have the ability to build in this new expertise. You always need to think ahead when building a facility. If anyone were to visit our facility now, they'd notice some corridors that seem to go nowhere.

And they do go nowhere – for now! But in the future, they will lead to new areas of capability. I would say that flexibility is especially important for ADCs because product demand his so variable. Some ADCs have a global demand of only 5 kg while others may be in the region of 300 kg or more. It's important to have a facility that can cope with those extremes, but be able to scale if demand changes in the future.

Location matters

One of the conditions of receiving investment was our presence in Wales, UK. But this also gave me a whole new appreciation for how difficult it can be to find an appropriate site for a facility – especially, as we didn't want to invest money on infrastructure unnecessarily. It was easy to find great sites, but they all required millions of pounds to install the electrical supply we needed. At almost the eleventh hour, the Deeside site became available. It had previously been used by Catalent for warehousing and distribution. It had space. It had power. And it had more space to expand into in the future.

Shortly after Catalent exited, it was raided by thieves for copper wiring. But that's another story… In short, never underestimate the challenges of finding a site and getting it up and running!

A blank sheet of paper can be a joy

We've been hiring a lot of staff recently – and we've been successful in attracting very experienced people. Some of them have chosen to leave big pharma and come work for us because we offer a blank piece of paper – the ability to do something from scratch and run your own process. Big pharma has been (and can be) very successful but there are some downsides; big companies tend to be systemized and procedural, so change does not come easy. At a new, smaller company you can employ what you have learned in the past; you can cherry pick ideas and build your own process – it's all been very exciting. It's also been stressful, of course! Often in the contract manufacturing market, everything comes down to price, which is unfortunate. However, we decided to focus on building up our technical capability before committing to a facility, which allowed us to showcase the skills and knowledge we have to offer. And we are delighted that clients have chosen to support us.

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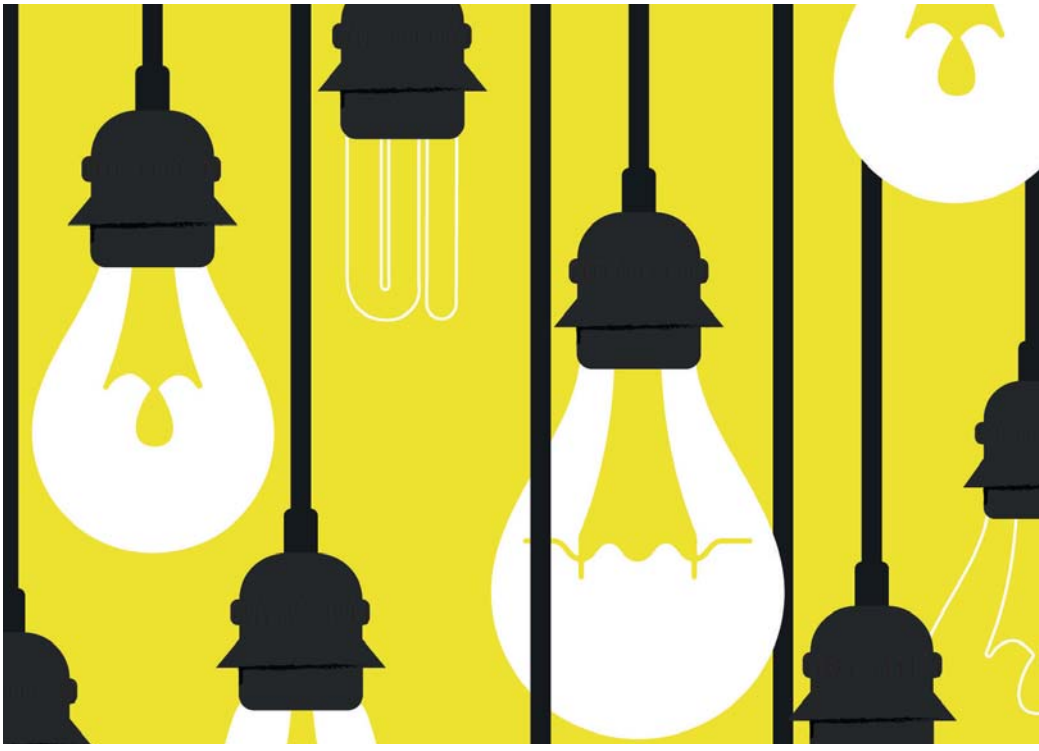
Bright SPARK

Academics have a role to play in the acceleration of biomedical innovation. And SPARK, a translational research program at Stanford University, is proving how important academicians are in slashing the time taken to bring novel therapeutics to market.

By Maryam Mahdi



Many academicians will, no doubt, be able to attest to the fact that years of research can seem to fall by the wayside as pharmaceutical companies refuse to take their novel discoveries for further development into therapeutics, creating barriers to the progression of translational research. It's well known that out of 10,000 new drugs developed at the bench, only one will often make it to the bedside, but are fixed ideas about what the drug development process should look like preventing this from changing? Aware that the starkly obvious cultural divide between academia and industry can create roadblocks to biomedical innovation, Daria Mochly-Rosen, George D Smith Professor in Translational Medicine, and Professor in Chemical and Systems Biology at Stanford University, set out to create a new initiative to help academics take their inspiring work further. Daria is the founder and co-director of SPARK at Stanford and president of SPARK Global.

What is the story behind SPARK?

I believe we, in academia, have a part to play if we want to serve patients worldwide. In 2006, I founded SPARK as a not-for-profit program at Stanford University to take promising advances in biomedical research and help translate them into new therapeutic options for patients. The campus-based program is based on collaboration between industry experts and academic investigators in the pursuit of novel drugs and diagnostics for all diseases, with a special emphasis on pediatric, maternal and neglected diseases areas. While being of significant clinical relevance, these disease areas are often left untouched in terms of drug development. The regulatory challenges and ethical issues associated with maternal and pediatric pharmaceuticals have perhaps left many in the industry with the feeling that the stakes were too high when it came to the development of new treatments for these areas of unmet clinical need.

For us, it is a moral imperative to address these issues. The needs of these patient populations are just as severe as any other patient group and they cause a significant burden for healthcare organizations worldwide. In 2017, it was estimated that over one billion people worldwide were affected by a neglected disease – one-sixth of the world's population!

By focusing on filling in the white spaces around these therapeutic areas, SPARK gained the attention of the Lucile Packard Children's Hospital at Stanford University's School of Medicine. They recognized the importance of what we were trying to achieve through the program and offered us funding. While the program is primarily funded by the university's medical school, the fund it receives from other philanthropic organizations and the National Institutes of Health have helped the program grow into what it is today – a research center with a success rate of over 50 percent when bringing potential therapies to the clinical trial or to a licensing stage. In comparison, the industry's success rate is 10 percent for projects at the same stage of development. A major aspect

of SPARK's ethos is to operate effectively without commercial incentives, as funding derived from these types of channels would create a conflict of interest for the dozens of industry volunteers in the program.

How has your previous experience influenced the development and evolution of SPARK?

Four years before the commensal of SPARK, I set up KAI Pharmaceuticals with my student, Leon Chen. KAI was a biotech venture focused on the development of novel therapeutics for cardiovascular diseases. The experience overhauled my perception of pharma and I gained a new appreciation for the complicated and intellectually stimulating work carried out by an industry, which I must confess I had previously viewed with a certain sense of scepticism! With SPARK, I wanted to provide other academic inventors the opportunity to learn from industry experts and push forward early ideas to benefit patients, in the same way I had at KAI.

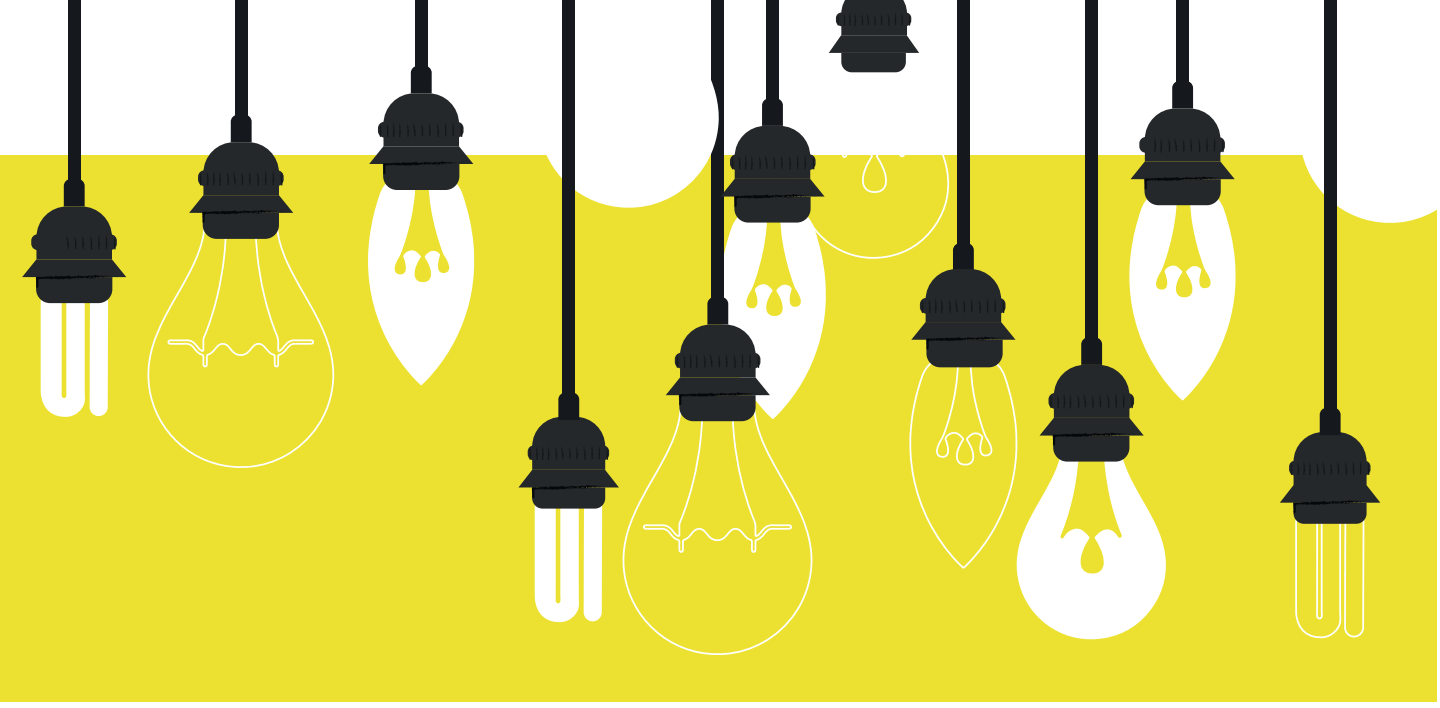
Our aim is to provide our SPARK scholar project teams (academicians whose projects we support) with enough exposure and insight from experienced pharma experts to help enhance their chances of success. Open to professors, clinicians, postdoctoral scholars, and graduate students, SPARK also offers graduate level courses on drug development, helping academics with a blue-sky approach to research to understand the highly regimented and regulated aspects of the commercial pharma industry.

How can established pharma experts also contribute to SPARK?

We have experts from the pharmaceutical industry who volunteer their time to the program, by sharing their stories of success and failure with our SPARK scholars. While they have no rights to the inventions developed through the program, their mentorship is crucial in helping move ideas from the bench to solutions at the bedside. SPARK hosts meetings, on a weekly basis, where the process of drug development and commercialization is taught to our SPARK scholars, and every fortnight, our project teams receive feedback on their work from advisory panels whose expertise lie in pharmaceutical drug development. Fostering these types of healthy working relationships, where ideas are shared between academics and many industry experts without the concerns or focus on financial return, defines SPARK and helps move translational research in a positive direction.

How does SPARK work with scholars?

Championing talent whose work goes unnoticed is integral to SPARK's DNA. Each year, SPARK selects between 10 and 15 scholars who are mentored under the program for two



years. The selection is carried out by a committee consisting of SPARK's team, pharma industry experts, and Stanford faculty members. The proposed projects are assessed on their ability to:

- Address an unmet clinical need
- Utilize a novel approach
- Be moved to clinic or be commercialized within a two year time frame

Scholars who join the program can only be described as powerhouses. So far, SPARK has launched over 30 companies, licensed 48 technologies, and led to 25 clinical studies – a great feat for both our scholars and the patients who will ultimately benefit from their work.

One of SPARK's scholars, Teresa Purzner, conducted research on medulloblastoma – the most common form of pediatric brain tumor. She has developed a potential therapy for the condition. Traditional treatment options for this form of tumor involve surgery, whole brain radiation and/or chemotherapy. This can result in intellectual and social impairment and deterioration of quality of life. Doing major basic research, Purzner identified that drugs which block CK2 – a protein kinase – may benefit children with this malignant cancer. One of these inhibitory drugs (and others from other project teams) are currently under clinical trial, but highlight the potential of SPARK Scholars for transforming the clinical landscape and disrupting the conventions that have seemingly been set in stone by industry players.

What have been some of SPARK's biggest success stories?

2015 marked the official launch of SPARK Global. As universities across the globe began to replicate the SPARK model within their own institutions, the need to properly organize became apparent. Currently, over 50 different institutions on all continents are involved in SPARK, forging partnerships to improve upon the number of therapeutics available for unmet clinical needs.

As just one example of how SPARK Global facilities help form connections in different countries, consider the Zika crisis, which drew public attention in 2016, and remains a major threat for children born to mothers bitten by the insect that carries this virus. The profound effects of this viral infection on the fetus results in microcephaly (small heads) and many other severe developmental issues. In an effort to help, researchers at SPARK Stanford are collaborating with SPARK Brazil and Brazilian scientists to develop a novel vaccine to combat the disease.

How do you think the work from SPARK could shift the drug development landscape?

Our aim is to encourage unconventional solutions to drug development. As academicians, out of the box risk-taking is what drives our progress and underpins our successes. Here at SPARK, we are developing creative approaches that are improving upon the current efficiency of the drug design process. Our academic and non-for-profit status facilitate us to enter meaningful conversations with organizations like the FDA about transforming the drug development landscape. We also aim to work with regulatory affairs bodies in Europe and Asia. We hope that these activities will allow regulators to hear alternative modes as to how novel therapeutics can be brought to patients faster.

My colleagues and I want our impact to be far-reaching – beyond the scope of academic publications. I believe that it is part of our social responsibility as scientists. We, as academicians, have the capacity to make a difference to patient lives and to complement other work that is strongly tied to the conventions of the pharma industry. We are two sides of the same coin and only by investing time in having serious conversations about the future of drug development and working together can we fulfill our mutual goal – to help patients.

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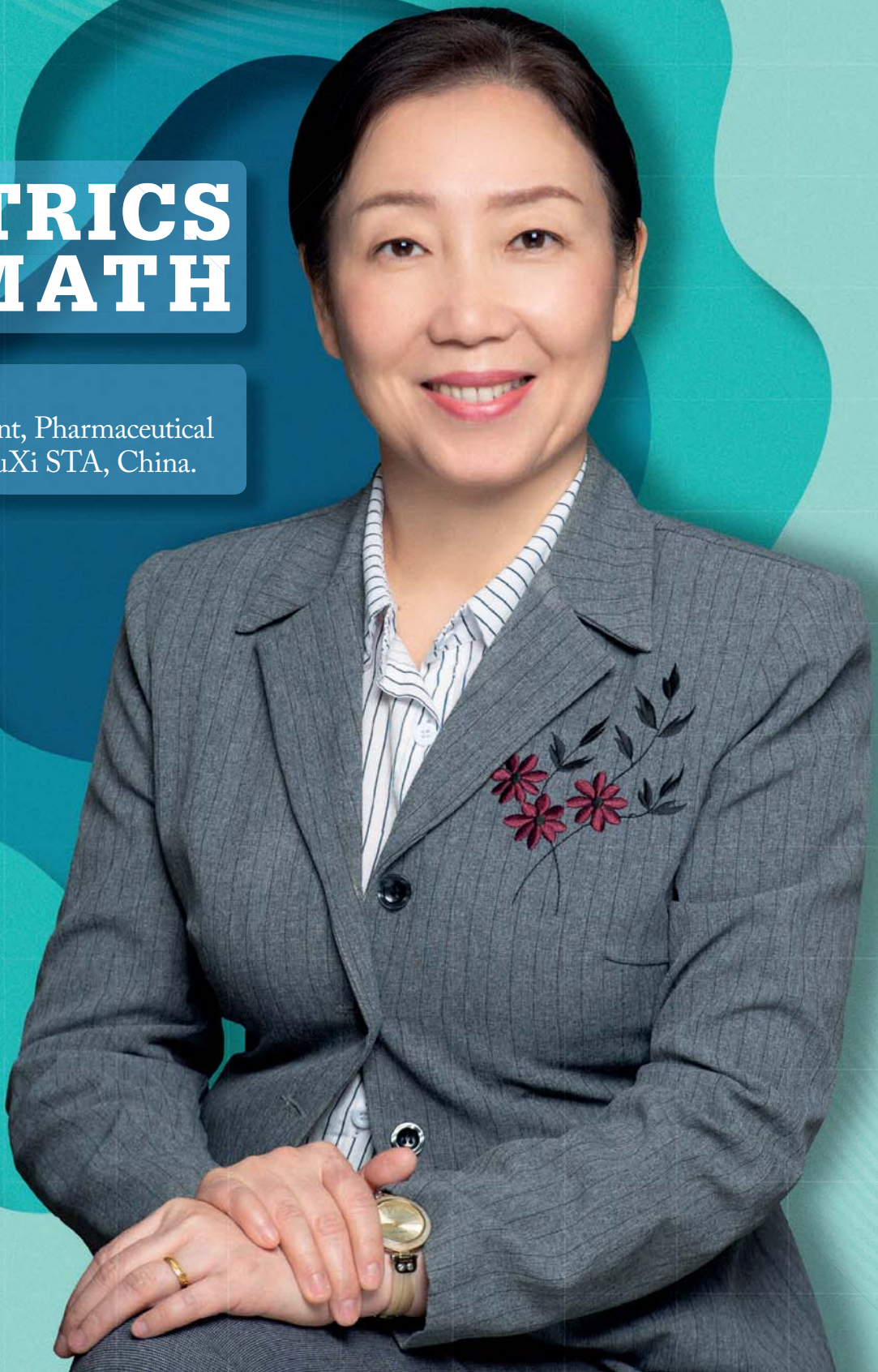
PEDIATRICS POLYMATH

Sitting Down With…
Jinling Chen, Vice President, Pharmaceutical Development Services, WuXi STA, China.



What was your focus in the early days of your career?

Following my PhD in physical chemistry, I worked in the US for over 20 years. My early career focused on drug delivery technologies. I really enjoyed the challenges in this field and I worked for a number of big players including AstraZeneca and BMS for about 10 years. I ended up with over twenty patents in drug delivery technology! But it's good to branch out to other areas. In 2002, I moved to Houston and worked for smaller pharmaceutical and biotech companies. The switch gave me the opportunity to diversify – roles are usually quite specialized in big pharma companies, but for the next 15 years I had the opportunity to work in drug development, research, clinical supply, analytical, NDA fillings and taking products to launch. I really enjoyed learning about different aspects of pharma development!

What is your role today?

Early last year, I was presented with an opportunity to return to China. Today I'm with WuXi STA, a WuXi AppTec company – it's my first time working at a CDMO! My role here is heading the pharmaceutical development division of Wuxi STA. We're around 400 people in the drug product division and we cover the full range of development – from the solid state characterization of the API, salt and polymorph form-screening, preformulation, stability evaluation, formulation development, as well as process development and scaling up for GMP supply of clinical trial materials commercial manufacturing. The responsibilities span R&D and GMP manufacture. So once again I'm branching out to new areas!

Sounds like you get involved with a bit of everything…

Indeed! WuXi STA is quite unique in having a service that is truly integrated across all aspects of CMC. My role is very varied. I'll often be in meetings with counterparts from API manufacturing or other departments. I've found that some unique ideas and solutions can arise from bringing such a breadth of experience and knowledge together. There's a lot of things I love about my role – and being surrounded by motivated people who genuinely want to make a big difference makes it even more enjoyable.

How have you found the move to the outsourcing sector?

The pharma industry has changed a lot over the years. When I was working for the large pharmas, they had substantial R&D departments in-house. Today, strategic outsourcing is much more common, so it was a good time to make the switch. Luckily, skills from pharma manufacturers are perfectly transferable to the contract services sector and it's interesting to see the industry from different perspectives. Having had my whole career in the US, I didn't quite know what to expect going back to China and working with the team in Shanghai, but I was taken aback by how dedicated everyone at the company is.

How did you become interested in developing medicines for pediatric populations?

Today, regulators are asking for specific plans for pediatric development. For example, the Pediatric Research Equity Act (PREA), passed by the FDA in 2003, imposed a requirement that companies test any new drug likely to be used in children in a pediatric population. Then in 2017, the FDA Reauthorization Act of 2017 gave the FDA the authority to ensure appropriate pediatric labeling of drugs and biologics. Similar regulations were also introduced in the EU in 2006. In my current role, we handle drug product development for our clients and considering the pediatric population is crucial.

What are the specific considerations when making medicines for children?

The first thing to remember is that children aren't just "little adults"; there are many specific considerations that formulators and developers must think about. The first is something that most parents are aware of: children are very sensitive to taste! This can make administering medicines as a parent very difficult! Differences in the anatomy and physiology of the infant and developing child can affect metabolism and the pharmacodynamics of various drugs and other xenobiotic compounds. There's also a large age range when we're talking about children – young infants and teenagers have very different needs. A conventional tablet may work for a teenager but not for younger children. When I've been involved with developing a pediatric drug, I look at the indication and the potential age groups that could benefit. If it's a wide range, it's a good idea to design at least two formulations – one liquid and one tablet or granular formulation. There are some good formulation options out there for children, including mini tablets and even formulations that can be sprinkled on ice-cream!

What would you like to see change in this area?

I would like to see the community learning from each other to advance pediatric formulation development in terms of the most effective dosage forms. I also favor the approach taken by some regulators to extend patent-life for drugs developed with pediatric populations in mind. However, pediatric medicines require special knowledge and technology – all of which costs money. The importance of compliance should never be underestimated, but ultimately we have a chance to make the lives of parents and children much easier when taking their medicines.

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