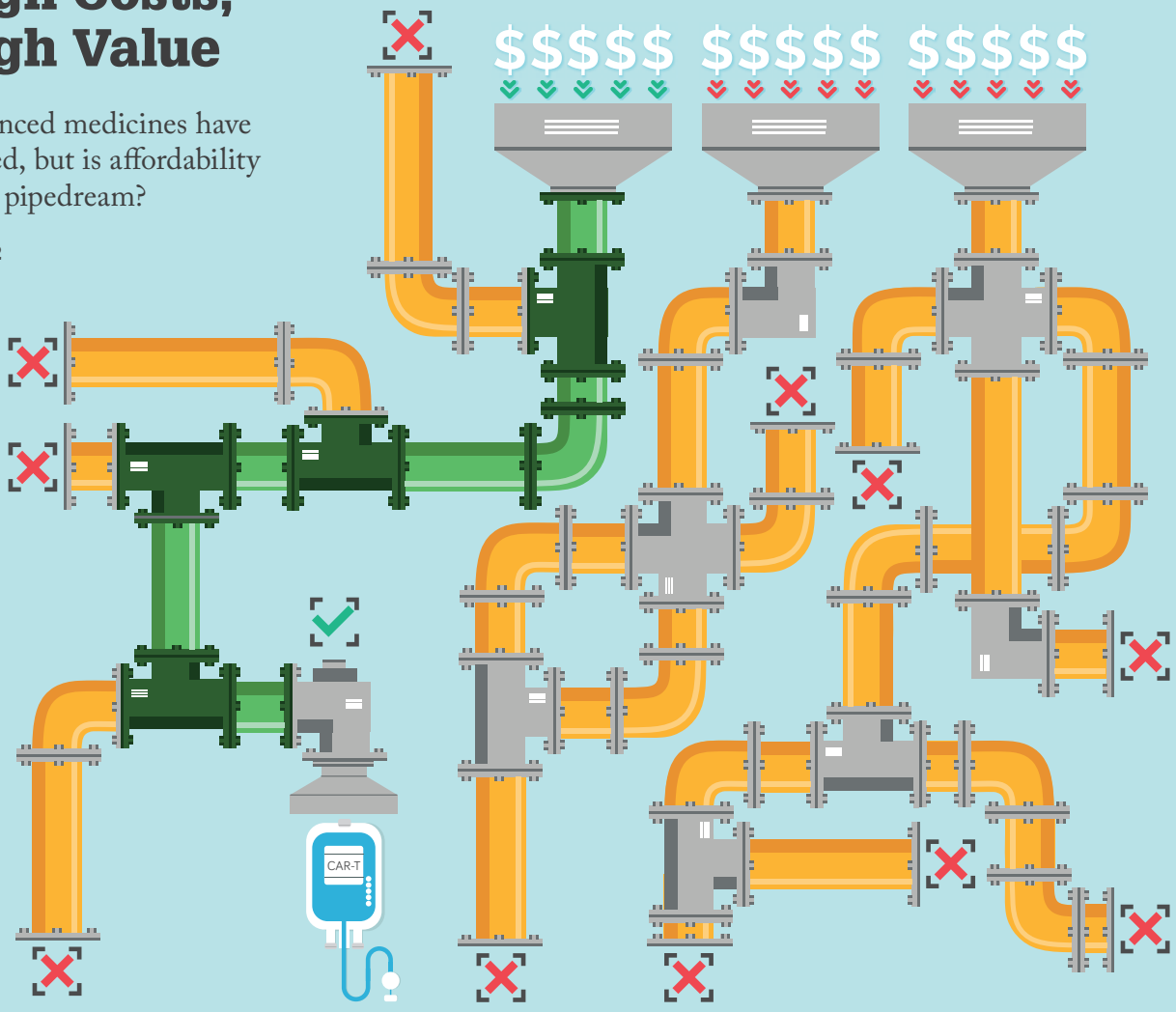
MARCH 2019 # 51

the Medicine Maker™

High Costs; High Value

Advanced medicines have arrived, but is affordability just a pipedream?



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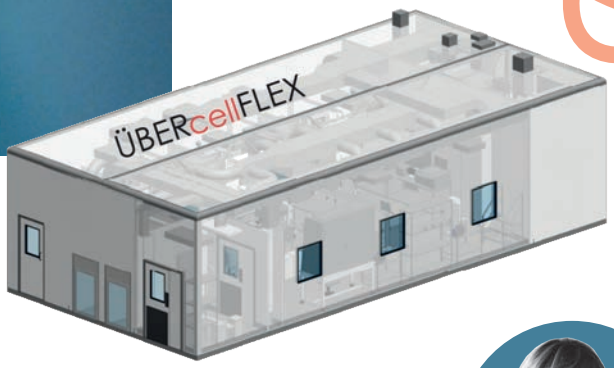

And the Winner is…

We asked you to vote on your favorite innovation from The Medicine Maker 2018 Innovation Awards – and the results are in. The top three technologies of 2018, as chosen by you, are:

1 Zydis Ultra Coating Technology by Catalent Pharma Solutions

2 syriQ BioPure by Schott AG, Pharmaceutical Systems

3 ÜBERcellFLEX by G CON and IPS

Look out for more information on these innovations in a future issue!

Remember Your Cleanroom Ps

Sue Springett, Commerical Manager at Teknomek, explains how proper planning and preparation prevents poor performance when it comes to cleanrooms. You can never be too thorough when it comes to planning the design of a cleanroom!

https://themedicinemaker.com/manufacture/remember-your-cleanroom-ps

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the Medicine Maker

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So Long and Thanks for all the Drugs

Scott Gottlieb prepares to leave the FDA after accomplishing much

You have probably all heard the news from the US: Scott Gottlieb has resigned from the role of FDA Commissioner (1). When he was first appointed, concerns were raised about his ties with the pharma industry, but Gottlieb will leave with his head held high. He has earned bipartisan praise, been highly active on drug pricing issues, helped speed up generic approvals, advocated for continuous processing and modern drug manufacturing methods, and been unafraid to call out abuse of any aspects of the system by drugmakers. And he has done all of this while still maintaining a good relationship with the industry. He's also been active on other important healthcare topics; just a few weeks ago, he insinuated that certain states with lax vaccination rules may force the hands of regulators, given the shocking rise of measles outbreaks in the US (2).

Gottlieb will leave in about a month, but recruiting his successor is likely to take some time – and in the unpredictable Trump administration, no one knows what or who will come next. At the start of his presidency, Trump caused panic after meeting with Jim O'Neill to discuss the FDA Commissioner job. O'Neill has no medical or scientific background and, in a 2014 speech, allegedly said, "We should reform FDA so there is approving drugs after their sponsors have demonstrated safety – and let people start using them, at their own risk. Let's prove efficacy after they've been legalized." (3)

Although some are concerned that Gottlieb was pushed out of the administration for his tough stance on tobacco products, the reason for the resignation appears to be the commute to and from Connecticut, and Gottlieb's desire to spend more time with his family (4) – a reason few can argue with. In this day and age, with so much technology that allows for remote and flexible working, it's a shame that organizations can't do more to support their talented workers – particularly those in highly demanding roles – to find a healthy work-life balance.

I wish Gottlieb all the best and hope that the next FDA Commissioner can pick up where he left off, continuing to encourage the industry to innovate and modernize without compromising on patient safety.

Stephanie Sutton
Editor

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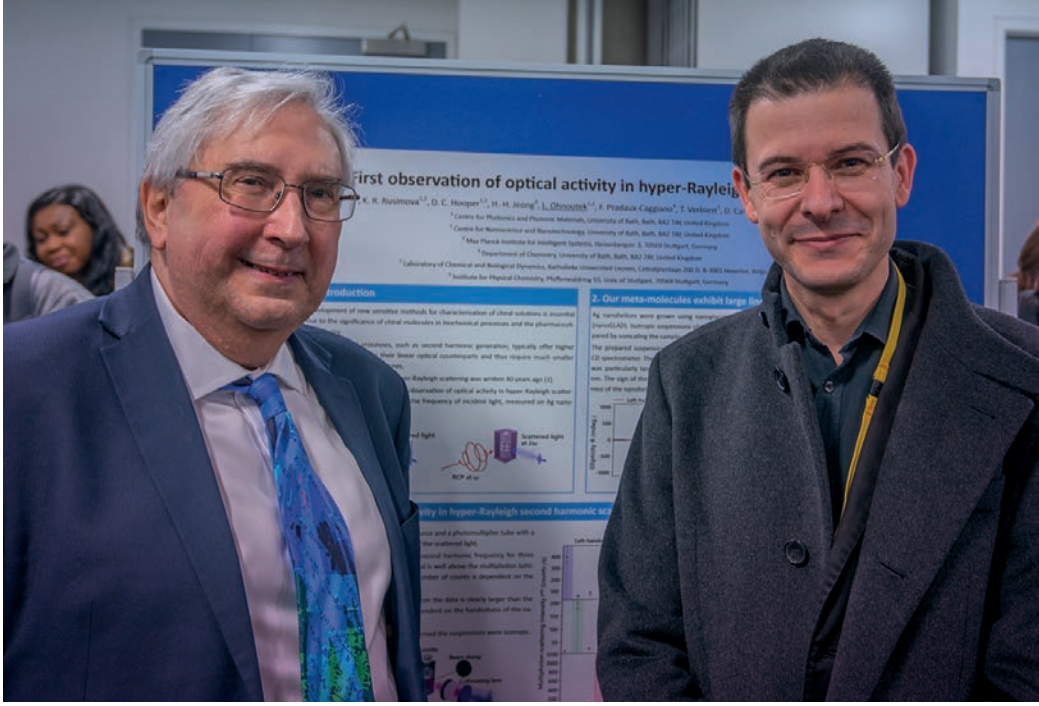
Upfront

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

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



The Color of Chirality

Forty years ago, it was theorized that chirality had a color composition that could be measured… and finally the theory has been proven

How can a guitar be distinguished from a violin? The physical characteristics of the two instruments are, of course, very different. But what truly separates the two is the difference that can be heard between them. If the same note is played on these instruments they will sound different because each instrument, in addition to the note played, plays a series of tiny notes called "harmonics".

Forty years ago, David Andrews, professor of chemistry at the University of East Anglia, theorized that chiral molecules (molecules which are non-superimposable on their mirror images) produced their own harmonics as they scatter light. But instead of relating to sound, these harmonics related to color. Andrews believed that the color changes observed in the scattered light would help distinguish which way a molecule twisted.

While the theory had a logical basis, it remained unproven. Scientists had attempted to prove the theory using natural molecules but the sought after optical properties of chiral structures couldn't be observed. Now, however, Ventsislav Valev, professor in the department of physics at the University of Bath, UK, and his colleagues have demonstrated that the physical effect does exist.

Using meta-molecules (tiny metal springs made of silver), the team was able to observe the light scattering effect. Though the same physical effect is possible using natural molecules, it is too small to detect or measure using currently available methods. The optical properties of the interactions between light and meta-molecules amplifies the effect, allowing measurements to be taken.

"The method we used is 100000 times more sensitive than conventional approaches to the measurement of chirality. Despite its simplicity this method is very robust and removes the possibility of producing false positive results," explains Valev. By dispersing nanoscopic silver springs in water within a glass container, the team were able to shine a laser at them. The circular polarization of the laser was changed and the resulting light scattering effect enabled the chirality of the molecules to be measured.

Valev believes that the volume of waste produced by the pharma industry in its

attempts to determine the chirality of drugs could be dramatical cut using the technique developed by his team. The sensitivity of the test also means that smaller quantities of product can be used in quality control tests. He adds that the process is well suited to lab-on-a-chip manufacturing that rely on microfluidics, the study of the behavior of chemicals through microscopic capillaries. These mini manufacturing plants facilitate chiral exploration and could be used to produce pharmaceuticals for personal consumption as and when they are required. Though current lab-on-a-chip devices cannot achieve this in a practical way, Valev envisions that it could be achieved using microfluidic methods.

Despite many having previously dismissed Andrews' theory, Valev was always convinced that the effect was real. He began to piece together the puzzle when he came across the work of Peer Fischer, Professor of Physical Chemistry at the University of Stuttgart, Germany. The academic had fabricated the silver metamolecules, which Valev combined with his highly sensitive experimental setup to visualize the color-changing physical effect. Valev now intends to apply a similar setup to natural molecules to demonstrate that the chirality of these structures can be measured.

"Science is the greatest intellectual adventure of humankind," says Valev. "It is an adventure that spans Millennia. Within this context, 40 years is not a long time. I feel greatly privileged to be part of this adventure with our team's contribution."

Reference

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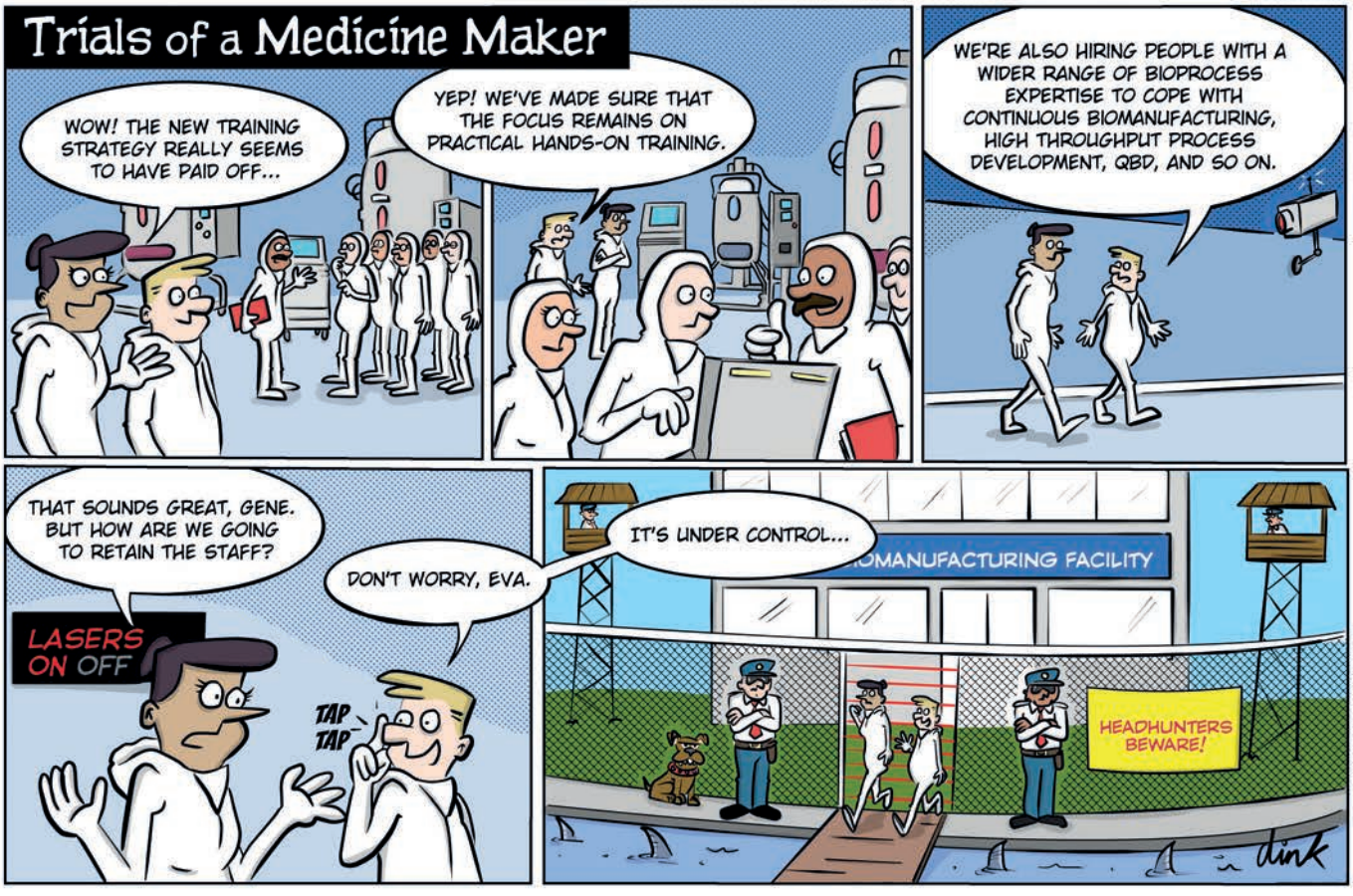
For more adventures featuring Gene and Eva check out our website themedicinemaker.com/additional-data/cartoons
If you have any ideas you'd like to see in future comic strips about bioprocessing then get in touch with us at info@themedicinemaker.com or look up #TrialsOfAMedicineMaker on Twitter.



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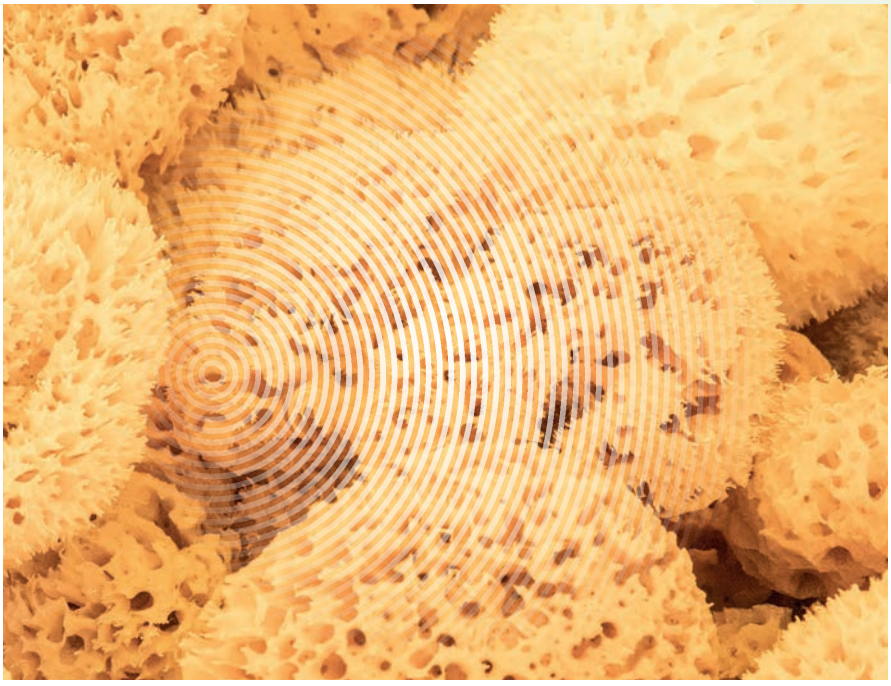
Soak it Up!

A polymer-coated device could help minimize the side effects of chemotherapy



Chemotherapy represents a lifeline to thousands of cancer patients worldwide, but the side effects can be detrimental to various organs within the body. Researchers behind the creation of a 3D printed chemofilter device – which they refer to as a drug sponge designed to "soak up" excess chemotherapy – hope their invention will transform the future use of these drugs.

The sponge was developed at the University of California, Berkeley, and inspired by a standard petroleum refining concept where absorbers are used to remove sulfur and other unwanted chemicals from petroleum. The device, developed by Nitash Balsara, a professor of chemical and biomolecular engineering at the university, and his colleagues uses a 3D printed cylinder and absorbent polymer coating to soak up unwanted chemotherapeutics. The chemofilter can be inserted directly into the veins of target organs, and the researchers have demonstrated that it can help prevent harmful side effects (1). Carbon Inc, a specialist company in 3D printing, is collaborating with the team to produce the customized drug sponges.

Initially, the technology has been designed to focus on liver cancer, an area the research team felt very strongly about. "There are tens of thousands of new cases every year and the condition is a massive public health threat. We already treat liver cancer using intra-arterial chemotherapy. However, you could use this sort of approach for any tumor or any disease that is confined to an organ," explains Steven Hetts, an interventional radiologist at UC San Francisco, who worked alongside the scientists at Berkeley to develop the device.

Early tests conducted by the team at Berkeley showed that the device was able to absorb up to 64 percent of doxorubicin, a chemotherapeutic, from the liver when injected at an upstream site in the livers of pigs. The cylindrical device was inserted into the pigs' blood vessels in the same way a stent would be, and remained in their veins for the same duration as the chemotherapy treatment. The fit of the device is crucial to its function. If poorly administered, poisonous chemotherapeutics flow past the sponge and potentially to other organs without interacting with the filter.

The next step, and real test for the technology, will be human trials, which are expected to begin in a few years. In time, the team also hope to apply the technology to other potentially dangerous drugs, such as high-powered antibiotics.

Reference

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RePURPOSED

Scientists develop a library to help teach old drugs new tricks

In sunny San Diego lies a library of drugs, which researchers are encouraging companies to exploit to repurpose old drugs for new needs. The open access drug catalog, ReFRAME, consists almost entirely of small molecules – all of which have reached the clinical development stage or undergone thorough preclinical filing – and is already showing results. Two compounds from the library have been identified as suitable treatments for tuberculosis and Cryptosporidium spp (1).

ReFRAME was developed by researchers at Calibr, a non-profit

arm of Scripps Research drawing on databases from Clarivate Integrity, GVK Excelra GoStar, and Citeline Pharmaprojects. The size of collection makes it conducive to medium-throughput assays and eliminates the need for drawn out assay optimization. "We have 12,000 compounds, of which 6000 are commercially available," says Arnab Chatterjee, Vice President of Medical Chemistry at Calibr. "The size of collection makes it conducive to medium-throughput assays and eliminates the need for drawn out assay optimization."

Chatterjee is particularly excited about the potential of the library to be used in the fight against neglected diseases.ReFRAME can be used to identify potential drug candidates by introducing compounds to disease-causing microorganisms. In the field of rare and neglected diseases, there is often less commercial motivation for research and development but the Calibr researchers hope that ReFRAME can be used to cut costs and timelines. Successful drug repurposing depends on the ability to translate in vitro data to proof of concept so having molecules that have already progressed to trials is a huge advantage. The Calibr team believe that it should be possible to take a screen to a clinical trial in less than 6 months.

To highlight the potential of the drug library, Chatterjee and colleagues focused on TB and Cryptosporidium spp. Cryptosporidium is a parasite which causes cryptosporidiosis, a diarrheal disease and a leading cause of death in children worldwide. With only one drug available for its treatment, the cost benefit of its use is questionable due to the negative effects the drug is known to have.

"The ReFRAME technology has given the scientists at Calibr the opportunity to find new compounds and make a difference to the treatment of disease," says Chatterjee. "We hope others will also take advantage of this library. Many people simply don't have the tools or resources to find new therapeutics. We can have the most impact by sharing our data and we're extremely excited about that!"

An open-access data portal (https://reframedb.org) has also been developed to share screen hits to encourage additional follow-up.

Reference

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Connecting the Data

A new AI platform aims to harness scientific data for improved drug development

Companies are increasingly investing in AI and machine and deep learning to open up new routes to innovation, but the technology is new and the data available in life sciences is vast – and many are not seeing the insights from AI that they expected. Elsevier has developed a new AI platform called Entellect that is specifically designed to cope with scientific data. The platform can contextualize and connect drug, target, and disease data. We speak with Tim Miller, VP Elsevier, Life Sciences Platform Solutions, to find out more.

How can using data more efficiently aid drug development?

Every drug development program generates massive amounts of data – and hidden within that data can be a new clue that might start a new drug program, or halt a drug program otherwise doomed to fail expensively. But so much of a data scientist's time is currently taken up with tasks such as cleansing, integrating and formatting data. Simply making data management more efficient could make a huge difference. Data is the lifeblood of life sciences R&D today and removing the obstacles to using it is critical in supporting the industry to deliver positive outcomes for patients. Whether realizing the full potential of precision medicine, identifying drug candidates for repurposing in rare disease treatment, or analyzing the safety and efficacy profiles of compounds in early R&D – the potential benefits through the use of deep learning platforms are significant.

What are the challenges of using AI in life sciences?

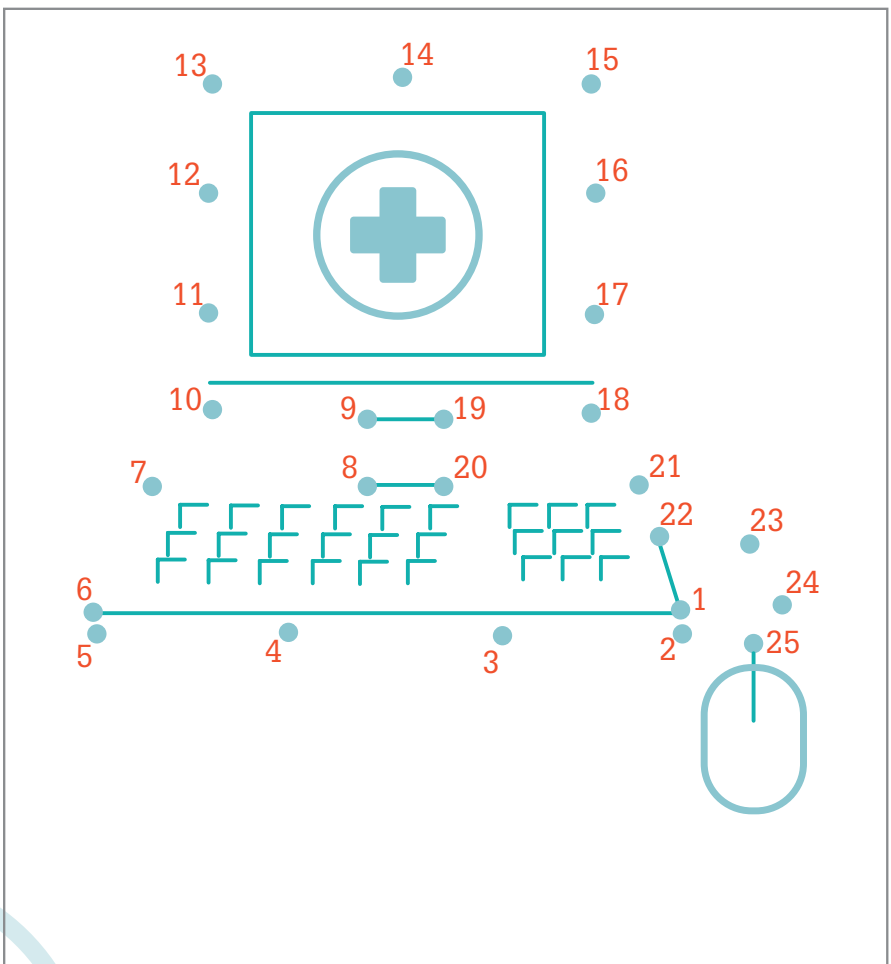
Life sciences is a difficult field in which to undertake AI because of the variety of different data, all captured in different ways for different purposes. These data then must be combined to provide a holistic view. We developed Entellect because many companies we work with expressed their frustration with other AI platforms. Few AI platforms are designed for life sciences – most platforms were initially designed for financial, automotive, and engineering problems. In my view, one tool which provides a singular experience cannot meet the needs of multiple different researchers – specialization is essential.

How does the Entellect platform work?

The platform is built on our heritage of rigorous data governance. Entellect links data from a multitude of sources, whether internal and external databases, LIMS, archives or public taxonomies. We hope that access to this data will allow researchers to produce far more accurate predictive models for drug R&D, including drug efficacy studies, risk-benefit analyses and pharmacovigilance. The platform has also been designed to simplify activities like text mining, data normalization, application of ontologies and mapping of ontologies onto multiple data sets. It's an open platform designed for data and application sharing.

How has the industry responded so far?

We've seen a really positive reaction. One customer has experienced success in helping to gather, cleanse and connect hundreds of thousands of different unstructured medical documents. The documents were provided in several formats, and Entellect was able to standardize the data to make it searchable. Users can search across various fields including drug names, targets and diseases, which allows users to rapidly access scientific information.



Full Disclosure

Oncologists frequently receive "gifts" from pharma companies, but how much is too much?

Do the financial relationships between oncologists and pharma affect clinical practice in inappropriate ways? It's a question that continues to be debated, and has been even more prominent since José Baselga, oncologist and chief medical officer at the Memorial Sloan Kettering Cancer Center, resigned after the research papers he had published failed to disclose millions of dollars worth of funds provided to him by the pharmaceutical and healthcare industries.

According to Aaron P. Mitchell, a medical oncologist at the Memorial Sloan Kettering Cancer Center, financial conflicts of interests (COI) between physicians and the drug industry are very common in the US, and a significant proportion of these interactions are oriented toward the promotion of existing drugs. In a recent study, he found that 70 percent of oncologists had received financial payments and/or in-kind compensation from the manufacturer of one or more of the cancer drugs they used (1). The study found that "gifts" varied from food, travel and lodging expenses, consulting fees, and honoraria.

"The collaboration between physicians and industry can be advantageous, particularly in the context of the development of new treatments. However, questions arise about what these relationships mean for the treatment of patients," says Mitchell.

The study found that the promotional nature of payments often resulted in oncologists using a particular company's drug more than alternative medicines, compared with oncologists who had not received any money.

An example outlined in the study is that of dasatinib, a highly potent BCR-ABL kinase inhibitor used for the treatment of chronic myeloid leukemia (CML). The drug is often prescribed over imatinib, a similar drug found in generic form, even though head-to-head comparison in clinical trials found them to be equally effective in preventing death from chronic-phase CML (2).

"With this choice, oncologists are choosing treatment options with greater out of pocket costs to the patient, that are not superior to alternatives," says Mitchell. "The financial consequences for patients are significant, and bring into question the ethical and moral acceptability of these relationships between oncologists and pharma companies. Physicians should be encouraged to rely on more independent sources of information when deciding which drugs to use."

According to Mitchell, policy changes are needed that maintain physicians' ability to work with the pharmaceutical industry for drug development purposes and prioritize areas of clinical need, while reducing ethically problematic relationships.

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Perusing the Pipeline

With cell and gene therapies being all the rage, we take a peek at some of the advanced therapies coming down the pipe – from preclinical studies through to phase III trials

Preclinical

- Scientists have developed a gene therapy that prevents axon destruction in mice. When an axon is damaged, either through injury or by certain therapeutic drugs, a protein called SARM1 becomes active, which triggers axons to self-destruct. This destruction likely plays an important role in multiple neurodegenerative conditions, including peripheral neuropathy, Parkinson's disease and amyotrophic lateral sclerosis. The researchers used an AAV vector to introduce point mutations into human SARM1 and inhibit its function. They found axon preservation similar to that observed in SARM1 knockout mice (1).
- An international team of researchers have used gene therapy to restore hearing in an adult mouse model of DFNB9 deafness – a hearing disorder that represents one of the most frequent cases of congenital genetic deafness in humans. Individuals with DFNB9 deafness are deficient in the gene coding for otoferlin, a protein essential for transmitting sound information at auditory sensory cell synapses. The researchers used a single intracochlear injection of two different recombinant AAV vectors to reconstruct the otoferlin coding region, leading to long-term restoration of otoferlin expression in the inner hair cells, and restored hearing (2).

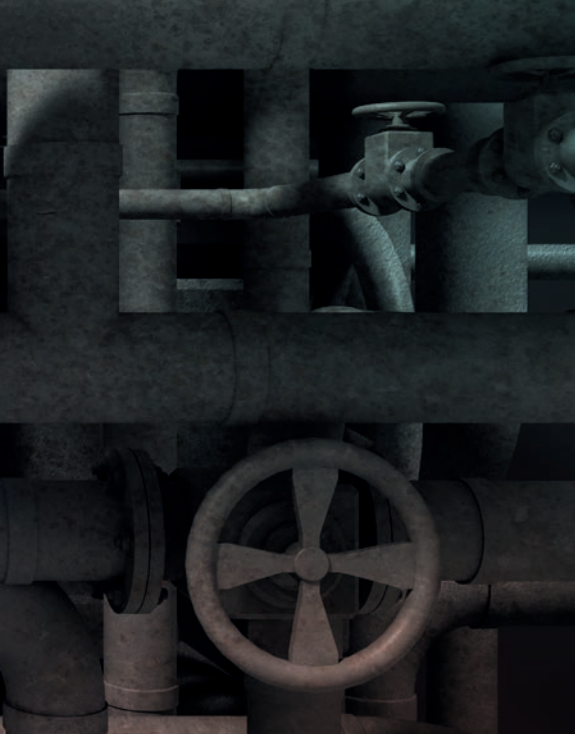
Clinical Trials

Phase I/II

- The first patient outside of China has been treated with a CRISPR/Cas9-based therapy. CRISPR Therapeutics and Vertex Pharmaceuticals' gene edited hematopoietic stem cell therapy, CTX001, received Fast Track Designation by the FDA earlier this year. The treatment involves collecting a patient's hematopoietic stem cells from bone marrow and genetically modifying them so that they produce high levels of fetal hemoglobin, which can protect against sickle cell anemia and β-thalassemia (3). The companies are currently recruiting for a phase I/II clinical trial in patients with severe sickle cell disease (4).
- Solid Biosciences are sponsoring a phase I/II trial to evaluate the safety, tolerability and efficacy of SGT-001, a gene therapy for Duchenne muscular dystrophy (DMD) (5). DMD is genetic disorder characterized by progressive muscle degeneration and weakness. It is caused by an absence of dystrophin, a protein that helps keep muscle cells intact. SGT-001 uses a recombinant AAV9 capsid to deliver a synthetic, shortened version of human dystrophin (mini-dystrophin).The aim is to support the production of a working protein similar to dystrophin (6).
- UK-based biotech ReNeuron has announced encouraging results from an early stage trial of its cell therapy for the rare blindness-causing disease, retinitis pigmentosa (RP). The treatment involves the injection of human retinal progenitor cells (hRPCs) – stem cells that have partially developed into photoreceptors – underneath the patient's retina. The aim is for those cells to integrate into the retina and fully develop into photoreceptors, replacing those lost to disease and, thereby, restoring vision. ReNeuron said all three subjects in the first cohort of the phase II part of the trial have demonstrated a significant improvement in vision at follow-up compared with their pretreatment baseline and compared with the untreated eye (7).

Phase II/III

- A pivotal phase III study is underway for AMT-061, an investigational gene therapy for people with severe



and moderately severe hemophilia B. AMT-061 uses an AAV5 viral vector to deliver the gene for a mutated clotting factor IX (FIX) called the Padua variant (FIX-Padua). This leads to a significant increase in FIX activity, which is compromised in hemophilia B patients and results to deficient blood coagulation and an increased risk of bleeding or hemorrhaging. The phase IIb results found that a single administration of AMT-061 increased therapeutic levels of factor IX (FIX) in all patients enrolled in uniQure's trial (9).

- Bluebird bio announced on February 21 that it plans on filing for European approval of Lenti-D in Cerebral adrenoleukodystrophy (CALD) in 2019. CALD is a rare condition caused by a mutation in the adrenoleukodystrophy protein (ALDP), which normally breaks down very long chain fatty acids (VLCFAs). The resulting buildup destroys the protective myelin sheath around nerve cells, which means nerves can no longer relay information to and from the brain. CALD usually affects boys between four and 10, leading to permanent disability and death usually within four to eight years. Lenti-D involves transplanting a patient's own CD34+ hematopoietic stem cells, modified to contain a functioning copy of the ABCD1 gene, which when mutated in CALD, results in production of nonfunctional (ALDP). bluebird bio currently has a phase II/III trial underway involving 30 patients (10) and a long term (15 year) follow up study (11).

Read more about advanced medicinal therapies on page 22.

References can be found online at: http://tmm.txp.to/2019/pipeline

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

Animal-Free; Risk-Free

If you or your supplier are working with animal-derived components then you run the risk of exposing patients to dangerous contaminations.

By Aaron Schieving, Vice President, Sales and Marketing at Lifecycle Biotechnologies, USA.

The risk of contamination is ever-present. Any given product, at any time – even when manufactured under cGMP and a robust quality management system can fall foul to the effects of contamination. The most at-risk products are those derived from biological sources, such as biopharmaceuticals, human cells, tissues, and cellular and tissue-based products (HCT/Ps). Therefore, donor tissues and cells can pose significant problems. "Title 21" of the FDA's Code of Federal Regulations (21 CFR Part 1271) contains requirements for screening donations of human cells and tissues for relevant communicable disease agents or diseases, such as human immunodeficiency virus, hepatitis B virus, hepatitis C virus, and human transmissible spongiform encephalopathy.

The screening of donor tissues and cells is a critical step in the lifecycle of HCT/Ps. Transplantation and processing of donor tissues and cells cannot occur if a donor is shown to have risk factors for, and clinical evidence of, infection due to relevant communicable disease agents and diseases after thorough screening.

And after such rigorous testing, why then would you risk the reintroduction of one of these communicable diseases into your tissues and cells? Though this question may sound absurd, the risk is real, especially for Creutzfeldt-Jakob disease (CJD).

CJD is a rare, degenerative, fatal brain disorder. It affects about one person in every one million per year worldwide; in the US there are about 350 cases per year. CJD usually appears in later life and runs a rapid course. Typical onset of symptoms occurs around the age of 60, and about 70 percent of individuals die within one year.

There are three major categories of CJD. Sporadic is the most common type of CJD and appears even though the person has no known risk factors for the disease. In hereditary CJD, the person may have a family history of the disease and test positive for a genetic mutation associated with the disease. In acquired CJD, the disease is transmitted by exposure to brain or nervous system tissue, usually through certain medical procedures.

Both sporadic CJD and acquired CJD can be acquired by ingesting or by being exposed to contaminated tissues and/or contaminated animal derived products. In some cases, CJD has spread to other people via grafts of dura mater (a tissue that covers the brain), transplanted corneas, implantation of inadequately sterilized electrodes in the brain, and injections of contaminated pituitary growth hormone (derived from human pituitary glands taken from cadavers).

Although 21 CFR part 1271 contains requirements regarding donors, the document does not address the risks of introducing CJD during the recovery or processing of HCT/Ps from contaminated animal-derived products. For this, you need to look to your suppliers.

Strong epidemiologic and laboratory evidence exists for a causal association between CJD and bovine spongiform encephalopathy (BSE) in cattle. It is possible for humans to contract CJD via contaminated animal-derived products from cattle affected by BSE. CJD and BSE are both prion diseases and there is strong scientific evidence that the agent responsible for the outbreak of BSE in cattle is the same agent responsible for the outbreak of CJD in humans. Currently, the most accepted theory is that BSE is a modified form of a normal protein known as prion protein. For reasons that are not yet understood, the normal prion protein changes into a pathogenic form that then damages the central nervous system.

Severe restrictions have been put in placed on the importation of live ruminants and certain ruminant products from countries where BSE is known to exist to prevent the disease from entering the US, but because the nature of the transmissible agent is not well understood, this is merely a means to mitigate the risk, not eliminate it.

The pharma industry has also put in place steps to help eliminate the dangers posed by contaminated animal-derived components, but only after they had to learn some hard lessons in this area following the heparin scandal.

In January 2008, the US health system authorities began to receive isolated reports of hyper-sensibility reactions in hemodialysis patients. Symptoms included hypotension, facial inflammation, tachycardia, hives, and nausea. Initially, enquiries focused on the filters and lines used in dialysis; however, research carried out by the CDC proved that all known cases had in common the use of sodium heparin. By February of the same year, the manufacturer of the sodium heparin withdrew all batches of the product, but not before some patients died.

"The contaminant was in the heparin material before it reached the supplier."

The FDA published the analytic methods to detect contaminated heparin batches in March 2008, which revealed a high degree of contamination. The FDA's investigation showed that the manufacturer and other suppliers had bought heparin from a single supplier, which, in turn, sourced the heparin from its factory based in China. The contaminant was in the heparin material before it reached the supplier. Since the Chinese factory sourced its raw heparin from various small suppliers, full traceability of the heparin supplies was not possible.

In response to the contamination issue, extensive revisions were made to the unfractioned heparin monographs of both the US and European Pharmacopeias, and it also led to more scrutiny of supply chains. In my view, today there is still the potential for pharmaceutical finished dosages to be contaminated with animal-derived products; for example, some APIs, starting materials and primary packaging materials involve the use of products/materials derived from animals:

- The use of proteins, enzymes, amino acids from animals used in the manufacturing of API and API starting materials.
- Primary packaging materials, such as like gelatin capsules, are derived from the fat of animals.
- For biotechnological products like serums, blood products and vaccines, source material can be derived from animals.
- There is also a possible risk of BSE contamination through equipment/utilities where biologically-derived products and/or products of animal origin are handled, such as culture media used in reactors for media fill studies, or reagents manufactured in a non-animal origin free facility.

The use of such animal-derived products is accepted, provided that the manufacturing process and procedures comply with the applicable regulations set by the World Health Organization (WHO), the European Commission and the FDA. However, where possible, the use of animal-derived products should be avoided when manufacturing products used to diagnose, treat, or cure patients. The best way to eliminate the risk of BSE and other contaminations resulting from animal-derived products is to maintain an animal-origin-free facility – and, importantly, life science companies should hold their suppliers to the same standards. If you choose to rely on a supplier that doesn't maintain an animal-origin-free facility, you are in danger of introducing contamination. For me, the choice is obvious.

It's Complicated

The potential market for complex generics is substantial, but navigating the FDA's guidance for proving "sameness" is a real minefield...

By Bérangère Tissot, General Manager at SGS Life Sciences.

Generic medicines are now an established part of the pharmaceutical supply chain and offer significant savings to health services, insurers and patients alike. More recently, biosimilars have entered the fray, and while the savings are not as great as with small molecule generics, they still help cut the costs of medicine. However, there is also a third category of product that falls between the two – the complex generic. These are products that may include complex: active ingredients, formulation, route of delivery, or even a mixture of ingredients.

The key to creating a new generic or biosimilar medicine and gaining regulatory approval is proving that it is safe and comparable to the originator product. For a small molecule generic, proving "sameness" between the two is relatively straightforward, relying heavily on a sub-set of well-defined analytical methods. Biologics are very different because the exact nature of the product depends on how it is manufactured, leading regulators to demand clinical studies that prove the biosimilar is functionally comparable to the reference product.

Many of the complex generics currently being developed are peptides – albeit less than 40 amino acids long – and proving sameness for the active ingredients can be tricky. The same often applies to other molecule types that can be considered "complex" such as polyamino acids (Copaxone (glatiramer acetate), which is a random combination of four amino acids) carbohydrates (which can also be sulfated as Enoxaparin or pentosan polysulfate), and naturally derived mixtures, such as oestrogens. Unfortunately, it is possible for an experienced generics company to approach complex generic submissions as generic ones, only for the application to be questioned by regulators.

European regulators tend to consider some of these complex generics products to be more like biologics (e.g., Enoxaparin), thus requiring clinical work. But the story is different in the US where regulators are looking for proof that the molecules are the same, similar to a small molecule generic. While draft guidances were recently published for Enoxaparin and glatiramer acetate, they only provide the general areas where sameness needs to be demonstrated – and no details on how to actually demonstrate it. There's also limited technical direction – certainly not to the same level as a general chapter in the US Pharmacopeia – the guidance simply says that equivalence must be proved. In some respect, this is in agreement with a lot of guidances from regulatory authorities. However, for biological products, other documents such as the ICH Q6B guidelines do offer a list of critical parameters and possible techniques to be applied when characterizing a protein. In the case of complex generics, there is very little documentation to be used and, when it does exist, caution needs to be exercised on how to put the information provided into use. For example, the guidance for Enoxaparin refers to complex documents such as a petition that spans over almost a decade, which discusses what might be required and refers to about 133 publications that readers will want to check. Much of this might be obsolete, having been superseded by more recent and applicable research.

For complex generic peptide APIs, the FDA specifies that physicochemical properties, primary sequence, secondary structure, oligomer structure, and biological activities must all be assessed. While many complex APIs may be comprised of chains of amino acids, they aren't proteins, so the typical protein toolbox isn't readily applicable. In fact, some are heterogeneous mixtures that may or may not have specific signatures or modifications, such as glatiramer acetate – for which there are no off-the-shelf tools at all.

For primary sequence or impurity characterization, there is a widespread, and mistaken, belief that mass

"The FDA is clear that orthogonality in the definition of each quality attribute is recommended."

spectrometry analysis will suffice, but this is rarely the case. If a peptide includes an unnatural amino acid that is an enantiomer of the naturally occurring version, mass spectrometry cannot unequivocally identify this because their mass will be the same. A technique such as chiral chromatography will be required in conjunction with sequence analysis if sameness is to be proved.

For these peptides, determining secondary and higher-order structures is quite complex. The techniques applicable to proteins simply aren't appropriate for smaller peptides, and the list of techniques suitable for this class of compounds is decidedly limited. How can these be used to create a comprehensive analytical strategy to prove sameness? To complicate matters even more, the FDA is clear that orthogonality in the definition of each quality attribute is recommended.

My take on this would be that the solution must use a lot of experimentally-driven evidences and an appropriate analytical strategy. The costs and timelines associated with this work are significant – and it would be easy for generics companies to embark on developing a complex generic, without fully realizing how much more challenging the process is, compared with a traditional small molecule. Even with a good analytical strategy at hand, there is the challenge of comparing it to the reference listed drug. Some of these peptides are formulated at extremely low concentrations – often less than a milligram per millilitre, and even down to the micrograms level. Vasopressin, for example, is typically formulated at approximately 37µg/ml, and calcitonin at 33µg/ml. Biophysical techniques to determine secondary structures are not applicable at such low concentrations and for such short chains. The formulation of the reference product also poses problems. Not only are they usually of low concentration, they are formulated with the inclusion of bacteriostatic ingredients, which are ultraviolet (UV) absorbents. Most secondary structure analysis techniques are based on UV methods, meaning these cannot be used on the formulated product.

New methods will have to be brought to the FDA that will work. But for the analytical scientist, this isn't as simple as finding the best method and running with it; it must also be demonstrated that the other methods won't work.

In my view, the key for all analytical sameness studies is in the preparation, planning and understanding of the technical and scientific challenges each complex generic API presents. Only if these are properly evaluated and defined in advance can any analytical package have a chance of being favorably looked upon. With the right planning, companies will be able to purchase enough reference listed drug (RLD) material for all phases of the study, design the fit-for-purpose studies for each of the quality attributes to be followed, and perform the experimentally-defined selection demonstrated-to-be-fit methods. Only then will this ultimately lead to straightforward analytical comparability studies.

NextGen Now: Delivering Tomorrow's Facilities Today

If cell and gene therapy products are to successfully reach patients and deliver transformative cures, then the industry will need more facilities capable of manufacturing them.

By Ryan McDonough

A huge number of advanced therapy medicinal products (ATMPs) are being developed, with many already in clinical trials. The growth predicted for these therapies over the next decade is significant because of their potential to deliver real cures rather than just managing a disease. A lot has been written about the promise of ATMPs (and I for one am really excited about what they offer!), but to bring these therapies to patients we need to manufacture them efficiently. Many ATMPs are personalized, which means that the manufacturing process must also be personalized (one batch per patient). These autologous therapies require very small-scale production as compared to the industry's traditional mass production facilities. It's clear that autologous ATMPs are quite different to what the biopharma industry is used to.

There is currently an ever-increasing demand and lack of capacity when it comes to facilities capable of manufacturing ATMPs – and specifically autologous cell therapies. At the end of 2018, there were over 1000 ATMPs in clinical trials (spanning phase I to phase III). Not all of these will make it through trials, of course, but for those that do, where will they be manufactured? Autologous ATMPs are not traditional biopharmaceuticals; they require different processes and manufacturing facilities. Because of this, many biopharma companies are looking to build dedicated facilities for ATMPs. Contract manufacturers are also looking to add capacity for ATMPs so that they will be able to capitalize on the market and attract new customers looking to manufacture ATMPs.

Given the growth prospects of the field, it's not surprising that a lot of companies want a slice of the ATMP pie. Many new partner companies are emerging, but over the next few years there will likely be a lot of changes and consolidation. Not everybody has the experience capable of navigating the challenges of the ATMP field. The keys to finding the right partners to enhance the delivery of these manufacturing facilities is to focus on those with experience, particularly with the regulatory expertise around facility design and construction. To the untrained eye, these facilities might look like glorified labs, but they are GMP facilities with very specific regulations around design, operations and supply chain management.

From paper to physical facility

At first glance, the job of a facility design and construction specialist is simple: design the facility, build the facility. There is a clear starting point on paper and a clear endpoint in terms of delivering the physical construction. But in my view, the job should go beyond this and encompass end-to-end project execution. ATMPs could transform health for many patients – and all of us involved in the field, including those of us specializing in facility delivery, have a role to play in helping this new era of medicine to reach its potential. The end goal is not to simply finish the construction of a facility, but to get the product to the patient. To do this, you need to design and build a facility that is capable of delivering the product safely, in the right quantities, and able to adapt to future demands.

Time and money can be saved by getting the facility design right at the onset. A holistic view is essential. You must understand the science, logistics, operations, manufacturing processes, regulatory requirements, and expected demand of your final product. This knowledge serves as the foundations of the facility and will influence the final building design. As with physical construction, if you don't build a solid foundation it will cause instability and inefficiencies later on, preventing future phases of the project from moving smoothly. During the design process, you also need to set out your target budget and schedule, and optimize based on that. Designing a good facility is not just about ensuring it has the right capabilities, but making sure it accommodates business needs and drivers. Over the years, I've seen far too many projects where the design progresses according to certain requirements, but then has to backtrack when the cost estimate is received. This wastes a lot of time and money because work has to be redone.

One of the biggest challenges with manufacturing ATMPs (and specifically

autologous cell therapies) is that the process is manual and labour intensive. Few automated technologies or platform technologies exist, and large numbers of staff are required, as well as large facilities to accommodate the need to scale out. This may all change in the future as the industry comes to grips with manufacturing ATMPs, but companies can't simply sit and wait for the process to be optimized or technologies to be developed. Facilities need to be built now – but the good news is that they can be designed for flexibility so that they can adapt to future trends and technologies. Operations improvement and simulation modelling can help manufacturers to understand what is happening in their facility, what improvements can be made, and how this might affect the facility down the road. Autologous cell therapy manufacturing is currently a very small scale and open process requiring high levels of classification and manual manipulations. In the future, however, manufacturing processes will likely become more automated, which means additional equipment and the ability to operate with less people, but higher throughput. Can you imagine that situation with the same floorspace, potentially doubling throughput? You need to think about future scenarios when designing your current facility. Predicting the future is difficult, but I think it is possible to make some fairly reasonable predictions about how facilities will look in the next five years.

Closed processing is one technology that is likely to change autologous cell therapy manufacturing as we see it today. We may also see innovations in isolator design and robotics. Given that human interaction is prominent in autologous cell therapy manufacturing, I expect we will see innovations focused on robotics that can replicate this interaction, while reducing the potential for human error. Removing the human element from the environment significantly reduces risk to product safety and, ultimately, to the patient. The main themes for innovation in the field will be how ATMPs can be manufactured and delivered safer, faster, more efficiently and cost effectively.

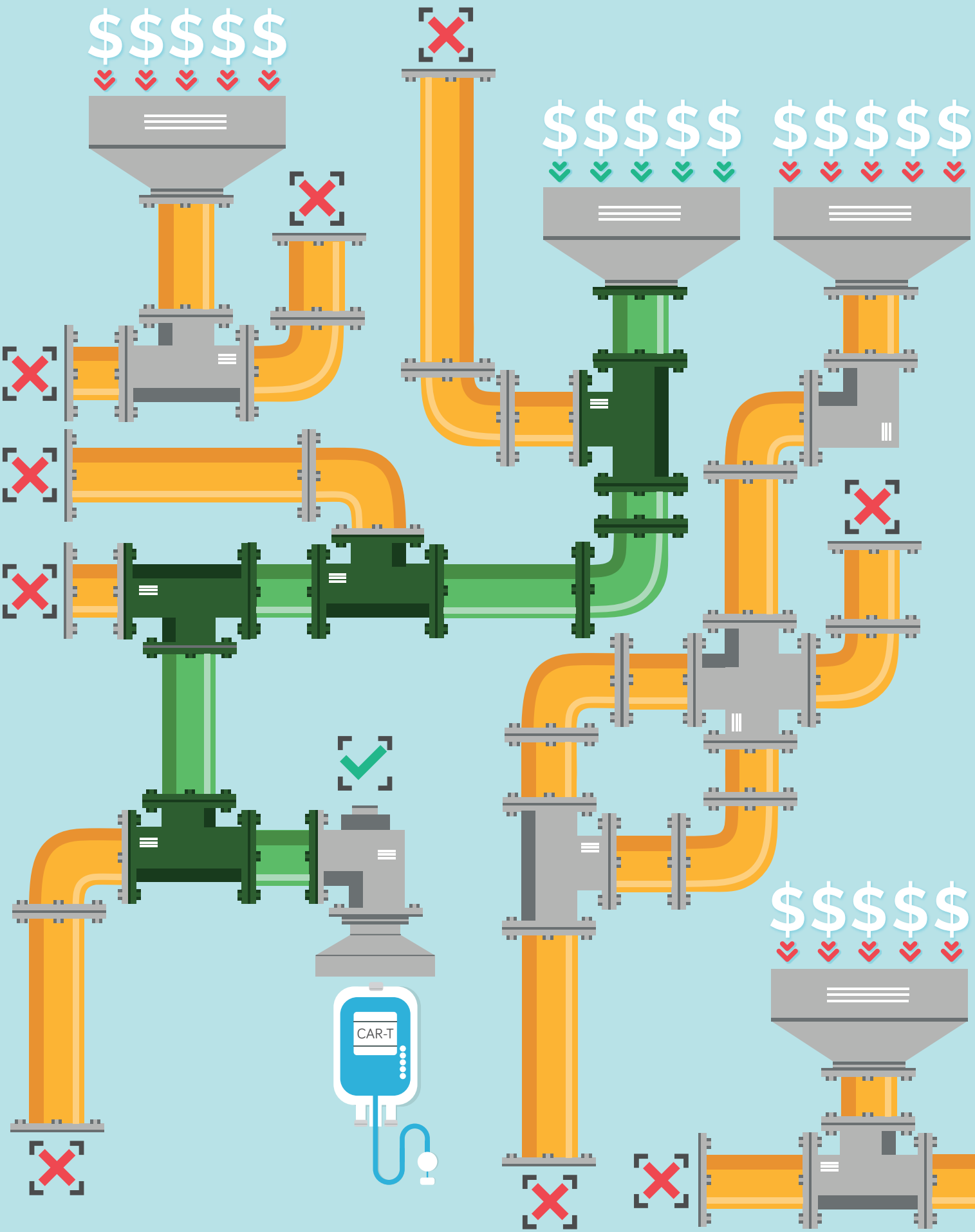
The fast lane

The ATMP field is changing fast and I would encourage companies to continuously review new technologies and trends. What we do not want to happen is that a facility based on what is currently available becomes the model for multiple facilities down the road. Five years from now, if we are still designing and building the same facilities that are being built today then I think we would be doing the whole industry (and patients) a disservice. This industry is highly regulated and there is a common saying that everyone wants to be the second to try out a new technology – no one ever wants to be the first because of the perceived risks! We need to be careful and not fall into the copy/paste facility cycle that was experienced in early biologics production.

But it's amazing to see the industry coming together to tackle the challenges of the field. Manufacturing companies, regulatory authorities, engineering, construction companies and others are all coming together to examine how we can get these therapies to market faster. The regulatory authorities have done a lot of work to develop new approval pathways designed to expedite access to patients, and the agencies have also been offering support and encouragement for manufacturers to use new technologies that can improve the production processes.

I think we have to take a risk and trust that if we are doing the right things and following the regulations then we can take advantage of new technology to make facilities more efficient and get these exciting cures to patients safer and faster. We need to be delivering tomorrow's facility today!

Ryan McDonough is Senior Associate, Biotechnology Market Sector Lead at CRB.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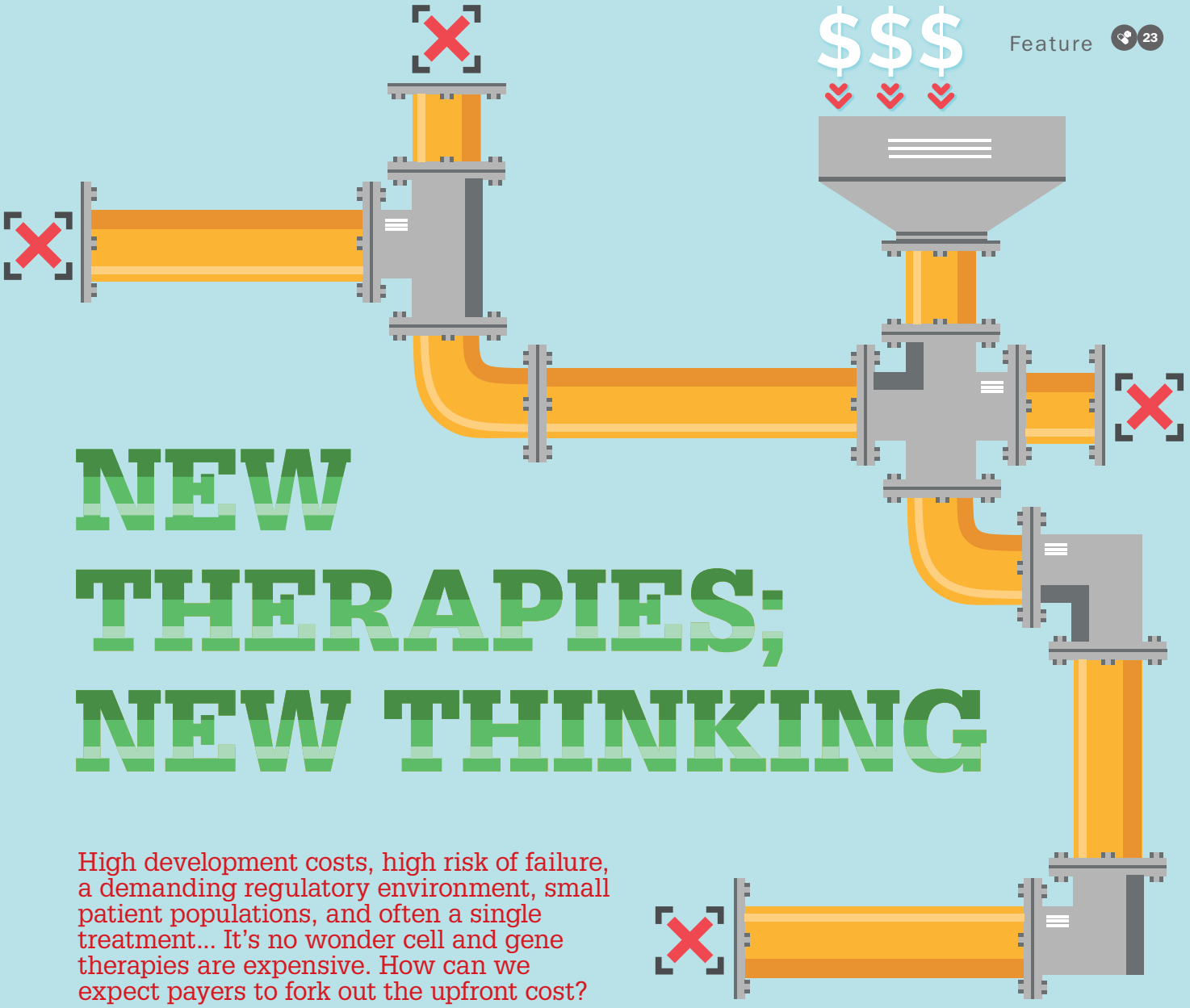


NEW THERAPIES; NEW THINKING

High development costs, high risk of failure, a demanding regulatory environment, small patient populations, and often a single treatment... It's no wonder cell and gene therapies are expensive. How can we expect payers to fork out the upfront cost?

Cell and gene therapies have been lauded for their efficacy – and some do, indeed, offer patients with life-threatening conditions and few options a chance of a cure. But developing a groundbreaking therapy isn't easy – or cheap. The combination of high development costs, high risk of failure, demanding regulatory environment, small patient populations, and few "doses" (often a single treatment per patient is sufficient) is a recipe for high prices – and perhaps failure. The world's first gene therapy, Glybera, was also the world's most expensive medicine. The million-dollar price tag proved too steep for payers; in fact, it has only been paid for and used commercially on one occasion since its 2012 approval in Europe, before being withdrawn from the market. What a waste of innovation...

The existing system of pricing and reimbursement was not set up for many of the current cell and gene therapies. And as an increasing number of products move through the clinic, it's imperative that manufactures and payers find a way to ensure patients have access

Here, we dip our toes into the murky waters of cell and gene therapy pricing by speaking with four experts: Dan Ollendorf from the Center for the Evaluation of Value and Risk in Health; William Milligan, Chair of ISCT's Business Models & COGs Committee; Ana Stojanovska, from Xcenda; and Nick Crabb from NICE.

THE PRICE IS RIGHT?

Health technology assessments find that many cell and gene therapies are more cost effective than existing treatments and/or managing symptoms with palliative care. But are healthcare systems and manufacturers ready to embrace evidence-based pricing to lessen the impact of upfront costs?

By Dan Ollendorf, Director, Value Measurement & Global Health Initiatives, Center for the Evaluation of Value and Risk in Health, USA.

What models do you use to assess cell and gene therapies in terms of their effectiveness and how this relates to pricing?

There really isn't a uniform model that can be used to assess the potential long-term cost effectiveness of cell and gene therapies because the data available differ in terms of robustness, the intended action, and how that relates to increases in life expectancy and quality of life. But I can give a few examples.

Some of the higher profile assessments we did at the US Institute for Clinical and Economic Review (ICER) – where I worked for over ten years – related to use of CAR-T therapy for a couple of different cancers: acute lymphoblastic leukaemia in children and non-Hodgkin's lymphoma in adults. The modeling was straightforward on the whole because the ultimate goal of any cancer therapy is survival. The challenge in this instance was that the data were new, so there's wasn't much follow up on the patient populations in the trials and we had to extrapolate what survival would look like over time. The models we worked with used different survival assumptions to see how the results of the modeling changed. Another challenge was that, like other cancer therapies tested in patients with few other treatment options ("last-line"), the trials had no comparator. In actual practice, however, clinicians will still likely try something, so we had to bring in data from other trials for comparison purposes.

This is quite different to some of the models that were done for cell and gene therapies in rare conditions, where the impact on quality of life was the main consideration. The first approved pure gene therapy in the US was for an inherited form of blindness in children. The challenge was that the primary outcome was new – the ability to navigate a low-light obstacle course. There wasn't an obvious connection to how that would improve quality of life as measured using standard instruments. The modelers had to make a variety of assumptions about how long the benefit would last and what the quality of life improvement would look like. In the end, we ended up with a range of results where we put boundaries around what cost effectiveness might look like moving forward.

The inherent trade-off is that because these therapies are of such great clinical interest, regulators want to get them to market as quickly as possible. But that means there isn't a lot of evidence for assessors to work with. That poses a challenge for the modeling, but we've done the best we can to try and understand, within reasonable boundaries, what the results might look like over the long term – recognizing that we should be tracking and monitoring to see if our models are reasonably accurate.

> "The results of our modeling in CAR-T, at least for these two initial cancers, make a relatively compelling case for the cost effectiveness of CAR-T."

How does an assessor take into consideration the benefit of a curative therapy balanced against the huge price tag?

Assessing the cost effectiveness of a curative treatment is difficult because there aren't yet good methods for understanding the "value of a cure." But methodologists around the world are starting to think about it more carefully with these potentially curative therapies becoming a reality. The approach we took with CAR-T is a sensible way to examine the problem. This would mean if survival reaches a certain stasis point, then we would consider that to follow the survival trend of the general population. This makes recognizing the value of a cure relatively straightforward, but the question of how to reimburse a curative therapy within systems that are set up to reimburse chronic therapies is an entirely different one.

Do healthcare assessments generally say cell and gene therapies are value for money?

The results of our modeling in CAR-T, at least for these two initial cancers, make a relatively compelling case for the cost effectiveness of CAR-T. We found that they were cost effective relative to standard chemotherapy. However, you might say that standard treatments are already expensive, so this is a false comparison. However, we also found that the CAR-Ts were cost effective in comparison to palliative care – in other words, no active chemotherapy and simply managing the patient's symptoms. This is a very strong case for paying for CAR-Ts, but the problem that remains for health systems is paying the high upfront costs...

Will cell therapies require different payment or reimbursement schemes?

The short answer is, yes! There are some interesting reimbursement schemes that are being discussed and/or put in place to try to tie reimbursement to whether a durable response and/or cure is actually achieved. I was part of a multi-stakeholder discussion in Canada on CAR-T cell therapies around requiring manufacturers to report quarterly updates on survival, so that payment could be adjusted based on response.

In the US, one of the manufacturers of a CAR-T said that payers and hospitals would not be charged if the patient was not able to receive an infusion – in other words, if there's some sort of manufacturing failure. They also said that there would be no charge if the patient did not exhibit a response by one month following treatment. There's been a lot of debate about whether one month is an appropriate time point, given that we're interested in a durable response, and discussions will continue. Overall, I do think some sort of outcomes-based contracting or managed entry scheme will be required because the cost is exorbitantly high upfront.

Is there a global consensus across different countries in how to assess these products?

There hasn't been a large number of assessments at this point, but there are some different approaches, depending on the country, particularly when dealing with high-cost therapies for very rare conditions. The challenge there, as Nick Crabb discussed on page 31, is that not only do you have a relatively small evidence base because the therapy is on an accelerated pathway with the regulator, but you also have very small patient numbers and, in some cases, outcomes measures that aren't standard.

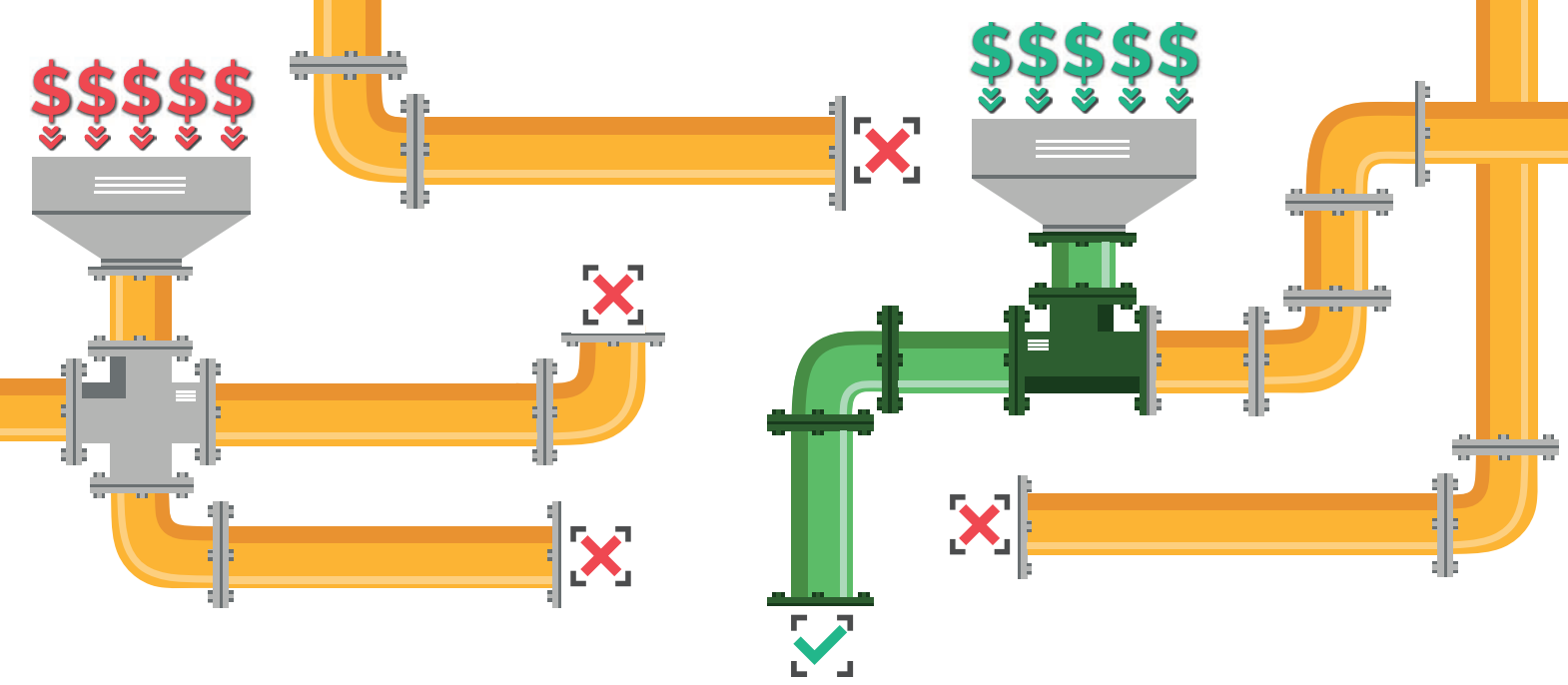
The Canadian approach isn't to try to understand the cost effectiveness, it's more about understanding the potential budgetary impact to the provincial systems and what the long-term outcomes might be. As Nick discussed, NICE in the UK will consider a higher cost effectiveness threshold for ultra-rare conditions. Although ICER does not change their threshold, they do report additional higher cost-effectiveness thresholds when the condition is ultra-rare with consequently small patient numbers.

What difference does the type of healthcare system make?

There are vast differences between a decentralized system like the US and others. For example, in the US there are certified treatment centers for specialized areas of care, and for cell and gene therapies we will need to create some sort of network of centers of excellence to refer patients to. In single payer system like the UK, there's the ability for that system to identify where those centers will be and how patients will be allocated to them. In the US, identification has really been up to the manufacturers, and there is greater scope for a national commercial payer to match up to those centers of excellence than for small regional payers. The additional expense for a small regional payer who may not have any centers of excellence near them to refer patients to across the country is a big challenge.

Do you expect to see a greater number of different schemes as more products are approved and for different indications?

Yes, especially in the US where the payer has to react to the price, as there's no real ability to start out with an agreed upon price like there would be with a formal HTA. In the US, there has been some discussion around the possibility of the price itself being adjusted depending on new evidence. At a public meeting, I pitched the idea to the manufacturers that perhaps they come out with a lower price at launch, based on the evidence available at the time of regulatory approval. But then as evidence accumulates, the price can go up or down depending on how well the therapy is working. I got an expected response: companies thought the approach would pose too much risk. But at the same time, at least in the US, the challenge is that the start-price is often nowhere near close to what anybody would consider good value for money, despite what economist might say. So we need to agree something on outcomes-based contracting to get a little bit closer to a reasonable price.



LET'S MEET IN THE MIDDLE

As long as payers recognize the value of a curative treatment and manufacturers are flexible with payment plans, patients will have access to cell and gene therapies.

By Bill Milligan, SVP Corporate and Business Development, Steminent Biotherapeutics Inc.; and Chair, ISCT Business Models & COGs Committee.

As part of the International Society for Cellular Therapy's (ISCT) Commercialization Committee, we've developed a business model for cell and gene therapies. We envisaged three key variables: willingness to pay, benefit of the product, and cost. We found that there's an ideal reimbursement market adoption zone where these three factors overlap to create conditions whereby payers will be willing to adopt a cell or gene therapy. Companies are spending a lot of money developing these therapies, with little to no return on investment until around phase II, where companies can partner. This, combined with the fact that the cell and gene therapies we've seen so far are only able to treat a small number of patients, resulting in high production costs, is prompting manufacturers to price their products very highly. But payers on the whole have quite low willingness to pay these high prices; and this is pushing these therapies outside the ideal market adoption zone.

> "Assuming the industry wins these arguments, the question becomes: can payers afford the upfront cost?"

The question for the industry is how do we modify price or willingness to pay to ensure patients have access to these therapies? One method is pharma economics – convincing the world that these therapies are actually worth it. We've seen from Dan Ollendorf (ICER) – and Nick Crabb also touches on this – that these therapies may be worth the high upfront costs based on standard measures of value – both to patients and to healthcare systems – used by health economists. And we mustn't forget the intangible benefits that a cure provides: you're literally changing someone's life, as well as the lives of their family and friends. This is perhaps especially true for pediatric patients. Some of these therapies are given to young children, who otherwise might not have lived to their teens, the chance to live a full life. And that is both incredible and valuable.

Assuming the industry wins these arguments, the question becomes, can payers afford the upfront cost? There are many people out there who would love to buy a house – they can afford the mortgage and they would save money in the long run over renting – but none of that matters if you can't afford the deposit. In the end, it comes down to affordability and this is where we've seen challenges with some of the earlier gene therapies with high price tags. Payers simply did not have the budget. This is where new pricing and reimbursement models will come into play.

Pay for benefits

In terms of reimbursement and pricing, the pay for benefits model – as discussed by Dan Ollendorf – could become key. In

WOUND CARE THERAPY

Osteocel by NuVasive in USA

$600

Dermagraft by Advanced Tissue Science in USA

$1,700

per application

Epicel by Vericel in the US

$6,000-10,000

per 1% of totapatient care & others

price higher because it is not used to treat a single wound site, but a large surface area of the patient's body

CARTILAGE-BASED CELL THERAPY

Spheroxby CO.DON AG in EU

$9,500-$12,000

ChondroCelect by Tigenix in EU

$24,000

Cartistem by MEDIPOST in S. Korea

$19,000-21,000

Carticel by Genzyme in USA

$15,000-35,000

INTRAVENOUS CELL THERAPY

Provenge by Dendreon and Valeant Pharma in USA

$93,000

Temcell by JCR Pharmaceuticals Co. Ltd. in Japan

$115,000-170,000

Prochymal by Osiris Therapeutics and Mesoblast in Canada

$200,000

CELL AND GENE THERAPIES

Kymriah by Novartis in USA

$425,000

per treatment

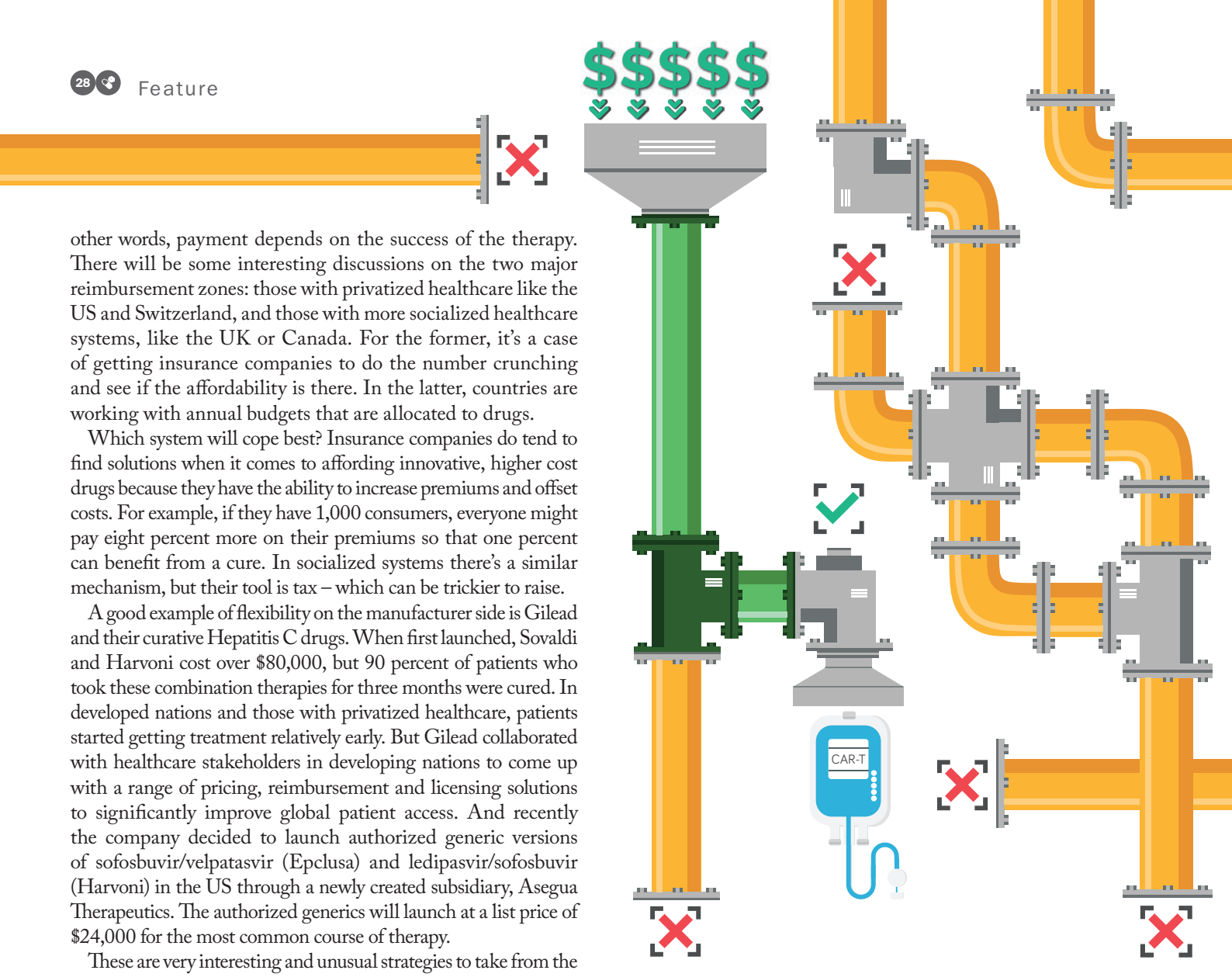
Yescarta by Kite Pharma in USA

$373,000

Strimvelis by GSK in EU

$665,000

(One of the world's most expensive therapies)



other words, payment depends on the success of the therapy. There will be some interesting discussions on the two major reimbursement zones: those with privatized healthcare like the US and Switzerland, and those with more socialized healthcare systems, like the UK or Canada. For the former, it's a case of getting insurance companies to do the number crunching and see if the affordability is there. In the latter, countries are working with annual budgets that are allocated to drugs.

Which system will cope best? Insurance companies do tend to find solutions when it comes to affording innovative, higher cost drugs because they have the ability to increase premiums and offset costs. For example, if they have 1,000 consumers, everyone might pay eight percent more on their premiums so that one percent can benefit from a cure. In socialized systems there's a similar mechanism, but their tool is tax – which can be trickier to raise.

A good example of flexibility on the manufacturer side is Gilead and their curative Hepatitis C drugs. When first launched, Sovaldi and Harvoni cost over $80,000, but 90 percent of patients who took these combination therapies for three months were cured. In developed nations and those with privatized healthcare, patients started getting treatment relatively early. But Gilead collaborated with healthcare stakeholders in developing nations to come up with a range of pricing, reimbursement and licensing solutions to significantly improve global patient access. And recently the company decided to launch authorized generic versions of sofosbuvir/velpatasvir (Epclusa) and ledipasvir/sofosbuvir (Harvoni) in the US through a newly created subsidiary, Asegua Therapeutics. The authorized generics will launch at a list price of $24,000 for the most common course of therapy.

These are very interesting and unusual strategies to take from the seller side, but promising from a global-patient access perspective. The dynamics for cell and gene therapies could be similar.

The key to lower cost

Although there are a number of variables feeding the question of affordability, there is a great deal of scope to reduce the price of these therapies by finding ways to reduce manufacturing costs. For example, autologous CAR-T cell therapies are inherently expensive to manufacture. To manufacture a single dose, several highly skilled and well-paid technicians are involved in the T cell isolation, activation, viral transduction for genetic modification, expansion, formulation, cryogenic freezing, and so on. The process is inherently expensive in its current form and introducing alternate transduction approaches, automation and closed processing will help to reduce manufacturing costs and, in theory, price. Perhaps future therapies will have a single universal donor that provides the cells and allows companies to manufacture thousands of doses per manufacturing run. These are the kinds of strategies we will see in play over the next few years as more breakthrough treatments advance to market.

It's a tremendous problem to have: how to maximize access to these amazing life-saving therapies. And it's incredible to think that we only mapped the human genome in 2000, and here in 2018 we've got genetically modified T cells that are delivering real cures for some cancers. I sincerely believe that we can evolve further and figure out how to make CGT therapies affordable for the broader population.

For manufacturers, once they have come up with a breakthrough therapy, they must either justify the price, find creative payment models, or go back to the drawing board and find a cheaper way to produce the product, achieving the ideal market adoption zone. I'm optimistic that manufactures see the need to be flexible with payment plans, and to find ways of reducing costs. And I'm also optimistic that payers see the value of potentially curative treatments. I do, therefore, believe that we will see cell and gene therapies treating broad populations of patients in need across the globe in the near future.

MONEY FOR VALUE

Manufacturers are increasingly open to value-based contracts for cell and gene therapies. Educating stakeholders, generating evidence and putting the patient first are key to getting it right.

Ana Stojanovska, Vice President of Commercial Consulting at Xcenda, has close to two decades of experience in reimbursement and health policy. Now she assists a number of biopharmaceutical companies with their understanding of the coverage and reimbursement landscape. Here, Ana shares her approach to, and experience of, working with manufacturers on their payment models.

Are manufactures open to alternative payment and reimbursement models?

Yes! There is so much scrutiny around drug pricing that we see manufacturers proactively approaching payers, making proposals and being part of the solution. While there are numerous challenges with designing and implementing alternative payment models, many of the newly launched gene therapies are taking the challenges to heart and showing not just willingness, but often leadership in engaging in some more innovative payment concepts. For example, the gene therapies that have recently launched in the US have all coupled their launch announcements with some sort of outcomes-based payment messages. These have varied in scope and detail, but generally have included arrangements with both public and private payers that tie reimbursement for the therapy to achieving certain pre-defined outcomes within a specified timeframe.

Is there a wider trend here?

Indeed. This is already happening to some extent. Additionally, Centers for Medicare and Medicaid Services' (CMS') recently proposed memo on how to cover CAR-T therapies nationally (1) can be seen as an additional step in this direction. In short, the proposal would mean that Medicare would cover CAR-T products for relapsed or refractory cancer indications and hospitals would need to enroll each Medicare patient into a national registry, ensure the patient meets all criteria and report on specific data points for these patients at baseline, treatment, 3, 6, 12, and 24 month intervals.

Though, for widespread and sustainable patient access, I keep coming back to what I think is the greatest challenge in paying for high-investment medications: the ability to recognize the value of the therapy over the term of the policy. That can be seen as a case for risk pools/reinsurance and/or special Medicare enrollment. We already have historical examples of how Medicare, for instance, has remained flexible to overcome high-investment therapy costs through the introduction of the End-Stage Renal Disease (ESRD) benefit. This could potentially also signal how other high-cost therapy could be covered in the future – the government could step in to create risk pools for insurance companies, have some sort of special Medicare enrollment or create an ESRD-type program for patients needing care. All of this would, of course, need further analysis, advocacy, and importantly, a more conducive political climate. Regardless, continued steps towards paying for value will allow patients to receive important and life-saving therapies.

> "We already have historical examples of how Medicare, for instance, has remained flexible to overcome high-investment therapy costs."

Can you give some examples of payment models manufacturers could, or should, be considering?

Outcomes or value-based contracting (VBC) is an example that seems to be most practical in the relative short-term. We've found that 40 percent of the payers we talk to and survey already have a VBC in place with pharmaceutical manufacturers, and this number is expected to rapidly increase. And while most of these existing contracts are for chronic conditions like diabetes, cholesterol or multiple sclerosis among others, it's only a matter of time before such arrangements for high-investment medications become more prevalent. Over half of our payer advisors tell us that they plan to implement a VBC for therapies like CAR-Ts or cell and gene therapies. Integrated Delivery Networks (IDNs) seem to be particularly interested in and taking steps towards making these contracts a reality.

We are also seeing carve outs and reinsurance options increasingly discussed for these advanced, potentially curative

READ MORE

The Medicine Maker has published two comprehensive supplements on cell and gene therapies. In 2017, five gurus discussed the exciting developments in advanced medicine, and what the field needs to move forward.

https://themedicinemaker.com/manufacture/advancing-medicine

In 2018, with CAR-Ts approved in both the US and the EU, we considered how to make cell and gene therapy manufacturing more closed and automated, to reduce the risks associated with human intervention and manual operations, as well as the problem of handling living breathing cells in transit.

https://themedicinemaker.com/manufacture/living-breathing-logistics

What will 2019 bring? We'd be delighted to hear your thoughts. Tweet us @Medicine_Maker or send your suggestions to: james.strachan@texerepublishing.com

therapies. One major national payer for example is carving out their review of CAR-T therapies through their transplant benefits and we have at least one manufacturer publicly talking about reinsurance as an option for their next generation products.

How would you approach working with a manufacturer on their payment model? What are the main things companies should be thinking about?

First, engaging early with decision makers to educate them on their advanced therapies is vital. The scientific breakthroughs for many of these potentially curative medications are incredible, but that does not equal automatic patient access because our payment systems have not evolved fast enough to accommodate the current advances. Education is one of the key steps in overcoming this barrier. The complexity of producing and administering a cell and gene therapy, for example, may involve multiple sites of care, multiple providers and multiple high-cost procedures, requiring an increased need for coordination and, from an access standpoint, an understanding of how the costs of the different aspects of the therapy will be covered. A thoughtful and deliberate effort is needed to educate stakeholders, including payers, on the pipeline, appropriate patient characteristics for the specific therapy and anticipated patient journey.

Second, generating evidence through data to support product value will support meaningful discussions with payers. The challenges to VBCs particularly for high-investment medications are many. For example, many of these advanced therapies are in rare diseases and small populations, which limits the ability of manufacturers to develop robust data sets and long-term outcomes that may be needed and desired. Further complicating the challenge is that often there is no prior treatment for a specific illness so there are no comparators or true understanding of burden of illness. Additionally, while payers say they desire to measure durability of benefit for a therapy, the large majority simultaneously acknowledge that they have limited or non-existent capabilities for monitoring long-term outcomes.

To address these challenges, manufacturers will need to have a detailed and comprehensive understanding of the patient journey from a clinical, reimbursement and care-coordination standpoint to ultimately design the types of patient experiences they want for their unique products. This requires aggregated data systems that allow the sharing of data between stakeholders, and use of registries to track longer-term outcomes.

Finally, manufacturers should be open to new approaches, arrangements and collaborations with the patient at the center of all decisions. The novelty of this space and the fact that there is no standard template for anyone yet creates a lot of opportunities to shape thoughts around decision making. This may require different

solutions for the short- and long-term. In my opinion, given the fragmented nature of the US healthcare system, scenarios that will be most feasible to become a reality in relative short-term are ones that gradually build on established reimbursement paradigms and are perceived as adding minimal complexities to what is already thought of as an already overly complex reimbursement system. Longer-term, we should be looking for additional thoughts around reimbursement and potentially changes to legislation to make patient access to these innovative therapies a reality.

Is current legislation is standing in the way of innovative payment arrangements in the US?

Many stakeholders agree that increased adoption of value-based arrangements for biopharmaceuticals has been significantly impeded by legislative and regulatory barriers. Many cite Medicaid Best Price and the Anti-Kickback Statute as examples of significant impediments to entering value- or outcomes-based contracts with payers. For example, Medicaid's "best price" rules are seen as increasing the cost of contracting and creating a financial incentive to limit rebates on applicable medications. The costs of running afoul of federal law are too high to make it worthwhile for many. Enacting safe harbors and carve-outs for Medicaid best price for example could increase the willingness of manufacturers to enter such non-traditional contracts.

And it's not just manufacturers that say this. Payers agree as well. In a recent (Dec 2018) Xcenda survey of nearly 50 managed care decision makers in the US representing over 300 million covered lives, over 90 percent of respondents say that exemption of purchases under VBC from federal best price requirements has extreme/strong or moderate impact on their ability to implement VBCs (same holds true for clarification of the anti-kickback statute that would specifically exempt VBCs with nearly 80 percent of respondents citing extreme or moderate impact). Exemptions of purchases under VBCs is not only the most impactful for payers, it is also the most urgent aspect that needs to be addressed to help with implementation of VBCs according to the same survey.

C&G THERAPY? THAT'LL DO NICELY

The striking combination of remarkable, long-lasting, clinical effectiveness and a hefty price tag presents a real challenge to health technology assessors considering cell and gene therapies. Nick Crabb explains how the UK's health technology assessment agency, NICE, is tackling the problem.

By James Strachan

The pipeline for advanced therapy medicinal products (ATMPs) is strong and the field has major potential for patients. NICE (The National Institute for Health and Care Excellence) in the UK wants to make sure patients have access to these remarkable therapies. But there are some major challenges to overcome to make that a reality. The first is working out how to pay for these therapies. The second is timely access for patients while evidence is still emerging, which it so often is for cell and gene therapies.

Nick Crabb, Programme Director, Scientific Affairs, NICE, UK, explains that there is a trend in Europe towards developing policies that increase the speed at which new products come to NICE and other health technology assessment agencies (HTAs) so that they are referred sooner in their development cycle, and with less evidence, with the aim of getting them to patients faster. "In England, this includes the accelerated access review and changes to the Cancer Drugs Fund in 2015," says Crabb. "UK-wide changes include the development of the regenerative medicine Expert Group, which has helped with UK preparations for cell and gene therapies coming to market, and the Early Access to Medicines Scheme," says Crabb. "Early access to medicines is something we have focused on managing."

The English Example

The high costs associated with ATMPs has forced HTAs to think differently about medicines. In 2017, NICE made changes to its technology appraisal framework intended to support financial sustainability. "At NICE, we use a cost-effectiveness framework where we capture the benefits to patients in quality adjusted life years (QALYs)," says Crabb. "But in 2017, we also introduced a budget impact test to support the sustainable introduction of new products. New medicines and technologies with a net budget impact of more than £20 million per annum

in the first three years of implementation may now be subject to commercial negotiations with NHS England, in addition to NICE cost-effectiveness analyses."

The aim behind the approach is to tackle the cost challenges – despite the benefits offered by some medicines the cost is simply too great for many government-funded healthcare systems. "In 2017, we also introduced a cost effectiveness threshold in our Highly Specialised Technologies Programme for the first time. The applicable threshold depends on the magnitude of individual patient benefit and is in the range £100,000 - £300,000 per QALY," says Crabb.

The combination of low evidence and high cost, however, has also presented other challenges to agencies like NICE. "There are a number of developments that we may see, including wider use of managed access arrangements to achieve equitable sharing of risks across stakeholders, post-marketing authorization 'real world' evidence collection to reduce uncertainty with time, greater emphasis on 'recommended with research' type recommendations in HTA/payer decision frameworks, and innovative pricing and reimbursement models." adds Crabb.

> "We found that the NICE appraisal methods and decision frameworks are fundamentally applicable to regenerative medicines."

In collaboration with the University of York, NICE has also been testing the applicability of its own methods and decision-making framework for disruptive technologies like ATMPs. "We developed multiple scenarios and put them in front of an expert panel experienced in NICE technology assessment. They were asked what decisions they would make if the scenarios were encountered in real appraisals," explains Crabb.

NICE wanted to explore the interplay between evidence maturity, price and payment methods. The hypothetical product chosen was a CD19 CAR-T cell therapy for treating relapsed or refractory B-cell acute lymphoblastic leukaemia (B-ALL) in children and young adults (this was done prior to the first FDA or EMA approvals). Based on a couple of small academic studies, the team developed two target product profiles (TPPs): a CAR T-cell therapy used "as a bridge" to hematopoietic stem cell transplantation (HSCT) and a CAR T-cell therapy used with "curative intent." To explore the impact of different levels of evidence, three hypothetical evidence sets were constructed for each TPP (minimum, intermediate, mature) providing six evidence scenarios. Within each of the six evidence sets, cost effectiveness analyses explored the impact of price discounts, payment models and discounting rates used in the economic analyses.

"We found that the NICE appraisal methods and decision frameworks are fundamentally applicable to regenerative medicines and cell therapies," says Crabb. "The work that the University of York did in quantifying and presenting clinical outcomes and decision uncertainty was key to the expert panel's consideration of the hypothetical example products. Crucially, the study revealed that where there is a combination of high cost, great uncertainty, but potentially very substantial patient benefits, innovative payment methods need to be developed to manage and share risk to facilitate timely patient access while evidence is immature."

The study also found that the discounting rate applied to costs and benefits was found to have a very significant impact on the health economic analyses of these types of technologies. This potentially means that if you discount too much, the fact that a product delivers benefit over a prolonged period means you end up weighing the evidence too far in favor of cost.

Since early 2016, NICE has issued guidance for a number of ATMPs. "These include Holoclar for treating limbal stem cell deficiency after eye burns, autologous chondrocyte implantation for treating symptomatic articular cartilage defects of the knee, and Strimvelis for treating adenosine deaminase deficiency–severe combined immunodeficiency," says Crabb. "NICE has also recommended tisagenlecleucel (Kymriah) for diffuse large B-cell lymphoma (DLBCL) and relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years; as well as Axicabtagene ciloleucel (Yescarta) for treating DLBCL and primary mediastinal large B-cell lymphoma after two or more systemic therapies."

Developments at NICE show that patient access for these important, yet often expensive, therapies is becoming a reality.

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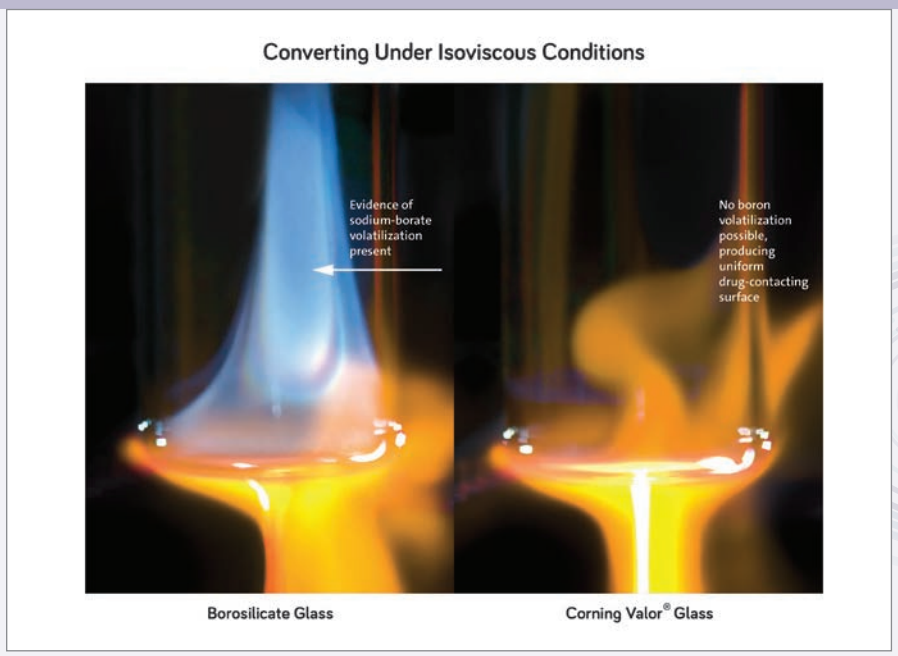
A Step Change in Pharmaceutical Glass Packaging Innovation

Corning's analysis into the root cause of glass delamination-related recalls identified boron as the culprit, explaining why process control of borosilicate vials only reduce the risk. As a result, Corning glass scientists developed Valor® Glass, a revolutionary, new aluminosilicate glass composition, developed specifically for pharmaceutical use to eliminate delamination.



Glass is ideally suited for parenteral packaging (1): it's chemically durable, able to survive high stresses and rapid thermal cycles, it's transparent, easily sterilized and formable into complex shapes. Historically, the industry used borosilicate glass compositions for sterile injectables due to their hydrolytic performance. But, the borosilicate glasses used for the last 100 years have been the source of numerous issues.

Glass delamination – the appearance of visible flakes or glass lamellae – has contributed to regulatory recalls. Beyond patient risk, delamination can be costly for pharmaceutical manufacturers. A glass supplier for the pharmaceutical industry notes, "For the respective manufacturers, this seemingly minor occurrence can then have costly consequences. One, single recall can cost a pharma company $250M dollars." (2)

Delamination in pharmaceutical glass has been discussed as early as 1953 (3), but until recently, the root cause of the problem was uncertain. Previously, sterile drug manufacturers didn't have many options. The industry had to accept delamination as a challenge without a true solution.

Converters of glass tubing to vials attempted to mitigate delamination with process control, which involves monitoring the process to produce vials with smaller heterogeneities (regions of non-uniform glass composition). This approach potentially lessens the risk for delamination; it does not eliminate the risk.

Corning continues a rich history of product innovation through robust understanding of fundamental materials science. "Several years ago, we were approached by a pharmaceutical company that wanted to understand how and why these defects occurred," said Dr. Robert A. Schaut, senior research associate, Corning Science & Technology. "This, plus the FDA's advisory (4) to sterile fill drug manufacturers alerting sterile fill drug manufacturers about the Agency's concerns with delamination."

Corning's analysis included fundamental understanding of the root cause of delamination and inventing a step-change in glass composition to eliminate it. Previous research found that regions of glass contained heterogeneities that were heavily enriched in sodium and boron. Boron is present in borosilicate glass to improve its chemical durability, but the chemistry isn't uniform because of the tube-to-container converting process. As a result, Corning studied the converting process and how it affects surface chemistry, particularly in regions that are in contact with the drug.

Converting a tube into its final shape includes a series of steps where the tube is exposed to direct flame and then cooled to form the neck, heel and flange of a vial. Type I borosilicate vials include oxides of sodium, boron, and aluminum in the glass network. Sodium and boron become highly volatile (unstable) when subjected to heat, and as the tubing is exposed to direct flame during the converting process, sodium and boron become volatile, evaporating out of the glass network into a gaseous state.

As the vial begins to cool, the sodium and boron deposit onto the sidewall and heel of the vial as sodium borate, and reactively incorporate into the glass surface. As a result, the actual glass chemistry of the vial's inner-surface is altered, which can increase extractables – and lead to delaminated glass particles – especially from the heel and bottom of the vial that comes into direct contact with a liquid drug.

This explains why enhanced processing techniques to control heterogeneities during converting cannot eliminate delamination. They do not address the root cause – boron evaporation. A carefully controlled-converting process

typically relies on an exhaust system to re-distribute volatiles, such as boron and sodium, more homogeneously into the interior of the vial. Factors such as greater wall thickness and vial circumference to heat mean more volatiles per vial, leading to greater propensity for heterogeneous regions in larger vials. And when some of these larger vial formats are analyzed, more delamination is seen. In the end, the risk of delamination cannot be eliminated if the glass formulation contains boron.

Delamination: Eliminated versus Controlled

Based on the root-cause analysis, Corning developed a boron-free glass, while maintaining a glass network comprised of elements used in Type I borosilicate vials, including silica and alumina – Valor® Glass. Corning has shown its aluminosilicate formulation eliminates delamination when compared to borosilicate. We've also seen that Valor Glass containers exhibit Type I hydrolytic performance, equivalent or lower extractables concentrations, and suitable drug stability.

"This shouldn't be surprising given that we haven't radically altered the formulation of the glass. Really, current glass should be called 'aluminoborosilicate,' since they are 70 percent silica and contain both aluminum and boron in modest amounts, said Schaut. "During the development of our aluminosilicate vials, we simply removed boron and adjusted the relative amounts of the other constituents."

A common question the glass manufacturer hears is, "Your glass is called aluminosilicate; shouldn't there be more aluminum in the extract?" In fact, high levels of aluminum in the borosilicate extracts are often a result of the heterogeneities ultimately caused by boron. "The amount of aluminum in Valor Glass' extractable profile is equivalent or lower than with borosilicate alternatives – and is far within safety thresholds," stated Dan Kramer, development scientist, Corning Science & Technology.

In addition, Valor Glass is designed specifically for pharmaceutical use, based on its extractables performance. Other glass manufacturers have published comparisons of extractables concentrations for type I borosilicate and aluminosilicate glass vials. These comparisons are silent on the actual aluminosilicate glass composition under test. This is important because there are a wide range of glass compositions that fall under this family. To be relevant, it is vital that testing for extractable concentrations use aluminosilicate pedigrees designed, specifically, for pharmaceutical packaging. Otherwise, the results are misleading. Using off-the-shelf aluminosilicate (as intended for handheld electronics) or borosilicate (intended for display applications) to evaluate its fit-for-injectable use is not an appropriate comparison.

"Corning's aluminosilicate is very different from aluminosilicates already on the market, as the extractables data shows; with the added advantage of eliminating the risk of delamination and associated product recall risk," said Kramer. "This also means not having to worry about implementing costly measures to control the converting process – Valor Glass can be converted using standard processes and is not vulnerable to delaminate."

Corning recently published a technical article supporting this in the PDA Letter (5). The data showed Valor Glass has comparable, and even superior, extractable performance when compared to Type I borosilicate glass, including aluminum extracts.

A step-change in innovation, solving a longstanding problem for the industry

If your glass vial contains sodium and boron, during the converting process, those elements will evaporate from the glass surface, and must travel somewhere.

"You may hope that your process is configured in such a way to reliably remove problematic vials. But you cannot test every vial; there's no method for assuring each vial produced is truly homogeneous and delamination free – these are sub-microscopic chemical defects that are impossible to screen out," said Schaut.

There are four steps from the formation of a heterogeneity to delamination. Corning notes those steps include, 1) Formation of heterogeneity, 2) Leaching, 3) Swelling and 4) Spalling off a delaminated flake. Because Valor Glass has uniform surface chemistry and does not form boron-rich heterogeneities during converting, it will not delaminate.

Over the course of the past two decades, the pharmaceutical industry has seen incredible advances in the development of new therapies, as well as in manufacturing technologies and processes. There is also a need for innovation in pharmaceutical glass packaging. The evidence clearly demonstrates Valor Glass represents a significant, and much needed, step forward for glass innovation.

To learn more about this topic, visit Corning's website: https://bit.ly/2HsQ4g0

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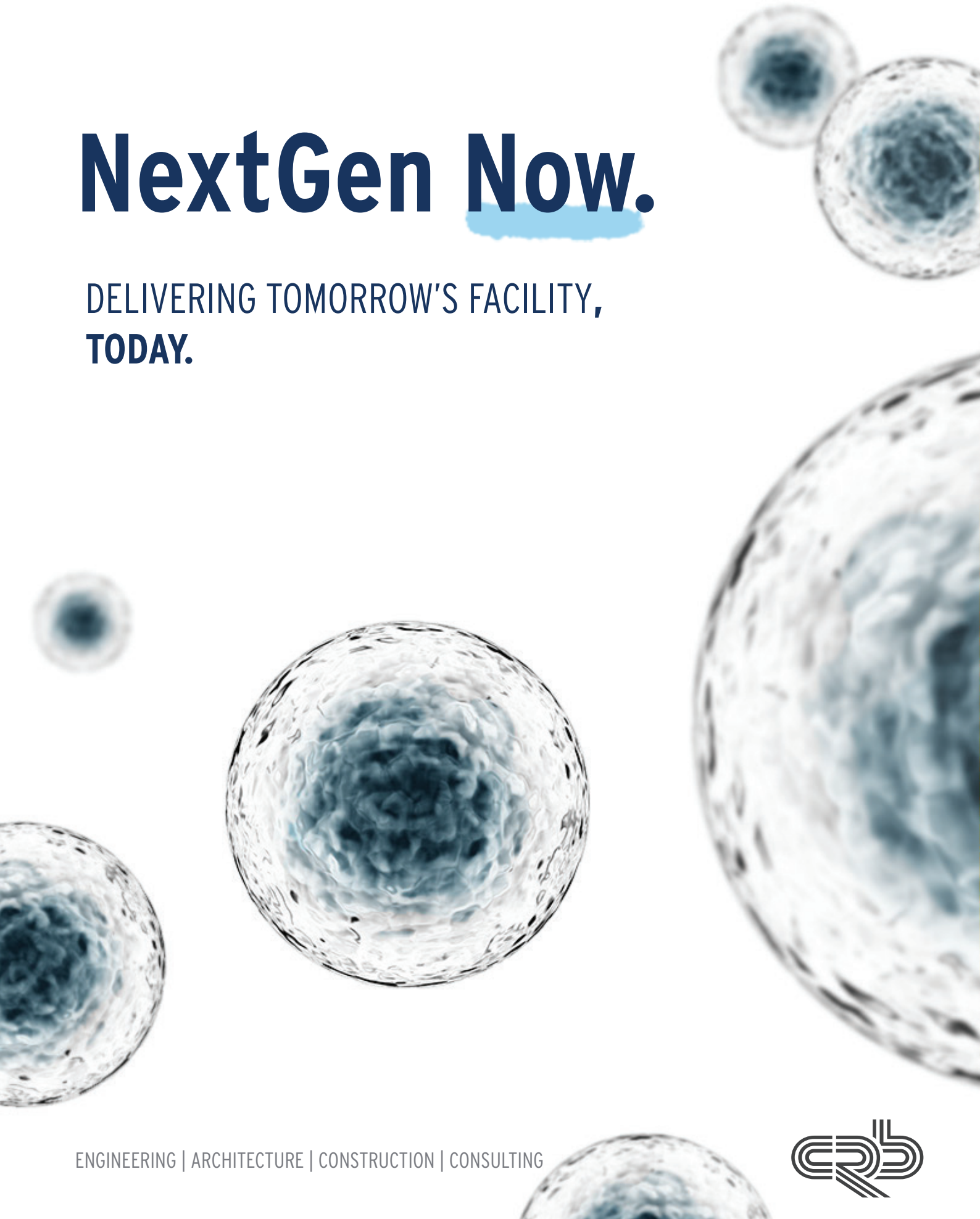

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Building a Business: Lessons Learned with Angela Osborne

Not allowing herself to be defined by stereotypes, Angela Osborne has created her own space in the industry and is helping the cell and gene therapy industry to bloom. Here, she shares the pivotal moments leading to the creation of the consultancy, eXmoor Pharma.

Don't let imposter syndrome hold you back

Pursuing a career in science never really felt like a choice – it was a calling. And, just like any passion, I willingly followed the path it took to making it an integral part of my life. English and history had no draw, but I loved the way science allowed me to explore the fundamental aspects of life as well as their practical applications. I made sure to take advantage of every opportunity that came my way. While completing my PhD in biochemical engineering at University College London, I was sponsored by Imperial Chemical Industries (ICI), which was the largest British manufacturer of its time. The experience was pivotal, but I thought that I might be better suited to a smaller company. Once I completed my degree, I applied for a job at British Biotech. While my peers sent out hundreds of job applications, I only sent off one. I knew I wanted that particular role; I'd worked with some of the company's founders during my degree as part of a summer job and I was lucky enough to be selected for the position!

As the only engineer employed by the company, I was afforded a great deal of responsibility from the onset. I was there for four years and I had the opportunity to manage my own team, work on the design and development of my own facility, and see one of our products enter the clinic.

Gender does not define anyone

I believe that many people let their differences hold them back from reaching their true potential. The notion that a person's gender, race or age can limit their ability to excel is unfounded. My next position in John Brown (later Kvaerner), a process engineering and project management company, was truly formative. I was the only woman among a sea of male engineers. Chauvinistic behaviors and ideas ran rife and I had to navigate the machismo-laden environment to prove my own competence. It wasn't an uncommon assumption that every woman who worked there was a secretary – and I was asked on multiple occasions to send out a fax on behalf of a male member of staff. But I knew I was as capable as anyone else there – a point reinforced by early promotion to a more senior position and strong reminders from my boss. My experiences have only made me more resilient and have allowed me to recognize the value I am able to bring to a role.

When I enter a boardroom full of men, I don't think of myself as the only woman in the group. We are all just people. We have a conversation to get through – an agenda – and my womanhood doesn't make me any less able to participate in it. I do believe that men and women have different ways of thinking and approaching problems; I think it is essential to have a balanced team so that more comprehensive solutions can be provided to any given problem.

I do believe that it's only human to succumb to feelings of unworthiness on occasion, but I strongly believe that focusing on personal ambitions rather than negative thoughts is key to anyone's success. A woman in a field dominated by men will stand out – and to anyone else in this situation I urge you to see it as your opportunity to shine!

Don't be afraid to take (calculated) risks

In time, I began to find being part of the corporate machine tiring – no doubt many of us do! Being pursued by larger companies for more senior positions wasn't thrilling; it was draining and the idea of being shackled to the bureaucracy and politics of the pharma industry did not appeal. I wanted to find a more meaningful pursuit.

My partner and I had always wanted a farm and our search took us to Exmoor National Park, where, in 2002, we bought a small piece of land and began rearing some animals. Purchasing this new property marked the start of an exciting new adventure, but there was also the fact that there was no work for us in the area! I decided I might like to become a self-employed consultant. I reached out to some colleagues – and eXmoor Pharma was born in a spare room at the farm.

Was it frightening? Yes. There was no money or company to fall back on if it didn't work out. We were alone. I had financial responsibilities including a mortgage. Then again, if we failed and I needed to find a new job then so be it. The regret of not pursuing the business would have been a far worse feeling. My colleagues and I wanted to change our lifestyles and have careers that fit round our individual passions and pursuits, and setting up the company seemed like the most logical way of making that a reality.

Multiple people have told me that we were lucky to be able to have taken such a huge risk, but the success we've had at eXmoor over the course of the last 15 years isn't a product of chance. We were a team of experienced individuals with the drive to do something different from the conventions set by the industry. And now, you couldn't pay me enough to go back to the type of work I was doing before!

Hold on to your integrity

When you initially conceptualize a business, it is more than likely that you won't be able to fathom all of the issues that come with


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running one. One of our greatest dilemmas was finding the right people to work with, and sometimes we had to say no because the companies offering us work weren't a good fit. We didn't want to be owned, we wanted to have our own unique voice to help support businesses. And that's difficult when you are just starting up and have no money coming in. But I think we were very good at evaluating opportunities and not being afraid to say no – this is easier when you are a consultancy because you don't have assets.

I recall that someone had once told me to write down a list of 10 places I thought eXmoor would work with – and then throw it in the bin, because the likelihood of them working with us was low. And they were absolutely right. Smaller companies were full of enthusiasm and ambition but lacked the money and resources to enable us to work alongside them, and we were totally averse to working with large pharma companies, despite the abundance of funds they had at their disposal. Medium-sized businesses proved to be ideal and working with them enable us to hold on to our ethos instead of selling ourselves to the highest bidder.

The rise of cell and gene therapies has caused a shift in the industry. It's been exciting for us to finally be able to work with smaller companies as they now have the funding to allow us to support them and help them affect change in the industry.

Change happens – don't resist

The initial focus of the consultancy was conceptual design of biopharmaceutical manufacturing facilities and associated manufacturing strategies; however, cell and gene therapies have ushered in an exciting new era in the industry. To stay abreast with the changing tides, many industry players – including ourselves – have needed to adapt.

Today, every science graduate interested in the pharmaceutical industry has heard of these therapies and appreciates the impact they will have on healthcare around the globe. But when I left university, biopharma was similarly in its infancy. When Guy's Hospital in the UK was interested in opening a cell therapy manufacturing facility, somebody recommended eXmoor to them. Though we had a great deal of knowledge about biologics and GMP, we knew little about cell and gene therapy technologies at the time. Despite this, I believed we were the best option available – no one in the industry had much experience with cell therapy – and eXmoor did know a lot about biologics and GMP. I made sure to let the clinicians I spoke to at the hospital know how I felt – and they gave us the contract.

First, we had to work on their first advanced therapy manufacturing platform. We developed the conceptual design for the facility and provided them with continued support throughout the project. Twelve years later, one of our

QPs still works at that facility, and cell and gene therapies have become eXmoor's main focus. Working on that project showcased how important the cell and gene therapy space is – and, since then, we've added more skills and looked at what is needed to convert research processes into manufacturing processes and how to integrate this into a manufacturing facility.

Changing gears and moving into a new field wasn't easy. And we lost some of our key players during that period of time for different reasons, but it allowed us to restructure the organization and introduce new directors to help smooth out the transition. We've been able to open our own labs in the last 18 months (Future Space, based at the University of West England), and it's an amazing asset for us because it allows us to work on process development for clients. It's also very useful for our consultancy team to see the latest equipment in the lab and understand how it really works. We'd never have been able to achieve this kind of growth and expansion without embracing the changing industry trends.

There are many skills gaps in the cell therapy field

A lack of skills in a particular field means there is a real opportunity to influence in a positive way. Much of the equipment used in the manufacturing of cell therapies is borrowed from the biopharma and medicine spaces, and so doesn't quite fit the requirements of this industry (yet).

How do we close processes? And how do we get to commercial scale manufacturing with a closed process and a reasonable cost of goods when you have a bunch of equipment that wasn't designed for that task? Much needs to be improved in the sector. Regulators are also still getting their heads around the field, but it's exciting to work with them, push the boundaries, and influence guidelines. I've read some articles indicating that regulators aren't open to innovation but that isn't my experience. I think regulators' reactions to the progress in the field has been excellent. They are very practical and are just as eager to see innovative change happen in the industry as we are. And that makes working with them all the more enjoyable.

"The advanced medicine space is exciting – and very rewarding."

I would say there is definitely room for improvement in academia. In our early days at eXmoor, one of our biggest frustrations was the secretive nature of academic groups. We saw the wheel of problems re-invented time and again because of their refusal to share information. At any given point, we could be called in by two or three groups with the same issues. It was in the best interest of all of these groups to create a community where they could share best practices and bring individuals across the industry closer together, and this is what sparked me to co-found the Advanced Therapy Medicinal Products (ATMP) Manufacturing Community (https://atmpmanufacture.org) in September 2010. The community has events, as well as working and advisory groups. We currently have 400 members, who, like myself, understand how crucial it is for stories to be shared and collaboration to happen so that the industry can be pushed in a more positive direction.

New science is exciting, but let's not get carried away

The advanced medicine space is exciting – and very rewarding. I have encountered remarkable people and companies throughout my career, but people often get caught up in the excitement of the projects. Rather than developing a full plan, and working from an end point back to a starting point with a clear plan to close the gap, they skip steps and then wonder why it all goes wrong. Often, consultants are approached to resolve problems that could have been avoided entirely if a methodical plan had been paid out and followed from the start. My advice? Don't get carried away. The highs and lows (and general chaos) of running a business mean that logical thought can be left by the wayside. Take a step back and try to be logical; think about how you will get from point A to point B. Once you have a clear picture of how to get there, the entire process becomes more straightforward.

Stay grounded

It's easy to get caught up in the competitive aspects of work. Meetings can leave you buzzing with the prospect of broaching new territories and making new industry connections. Coming home to administer medicine to a sick animal on the farm is a whole different kettle of fish! It reinforces the fact that work isn't everything. That said, it's fantastic to be working in such an inspiring field. Cell and gene therapies are life and death technologies that are genuinely making huge differences for patients – and we're seeing the results of these treatment types in real-time. Sometimes our QPs come back from approving a batch of treatment that is just about to be released. We're all acutely aware of the fact that the patient is waiting for the treatment, so the critical nature of the situation is brought home. In the general pharma industry, where there is a detachment from the real people using the drugs, you don't have such a strong connection. For me, motivators other than profit and acclaim give real meaning to my work.

Angela Osborne is Managing Director at eXmoor Pharma, UK.

The Upstream/ Downstream Process Balancing Act

Early collaboration and open communication between upstream and downstream are crucial to ensure a consistent end-to-end bioprocess.

By Serena Fries Smith and Hunter Malanson

Traditionally, bioprocess development is split into "upstream" and "downstream" functional groups. There are individual challenges associated with the development of both pieces of the process, with upstream focused on producing quality product, and downstream on purifying it. While these two functions rely on each other to be fully successful, they frequently work in parallel – yet separately – to meet the aggressive timelines of the program. This approach may allow for some efficiencies during development, but if the two teams are not working together, it can also create problems.

Developing a robust process

During downstream development, scientists are focused on a number of unit operations. For a therapeutic protein, these processes would start with a primary recovery step – where the cells and debris are removed. The clarified material would then move through a variety of subsequent processing steps including buffer exchange, material hold, viral inactivation/filtration, and chromatography – which are required to remove process impurities and isolate the protein of interest. Each individual step has critical process parameters (CPPs) that need to be monitored and controlled to ensure the critical quality attributes (CQAs) of the intermediates and purified protein will be achieved at the end. But the biggest factor to ensure a consistent and successful downstream process is not even one that the downstream team can control: it is the consistency of the upstream harvest material.

"If you think of a manufacturing process as a chain of inter-connected blocks, with each block representing a specific unit operation, changes to any block or series of blocks can have lasting and unpredictable consequences to blocks further down the chain. In that sense, upstream processes have a profound impact on the reproducibility and performance of downstream processes." – Pratik Jaluria, Executive Director of Process Development and Manufacturing at Adverum Biotechnologies.

Development of a robust and consistent downstream process must include the ability to understand and balance the output from the interconnected upstream process. During upstream production, we tend to overly focus on product titers, but other factors such as cell concentration, cell viability, and various product quality characteristics may be impacted to achieve those high titers. And these upstream factors will most likely impact the subsequent recovery and purification process steps.

As an example, one NS0 process developed was initially harvested at a viability of 30 percent to maximize the antibody titer. Unfortunately, this low harvest viability resulted in significant problems downstream and caused very low cumulative process yields. Through discussions with the purification team, it was decided that a new harvest viability specification of greater than 50 percent would be used for this process. Upstream, there was a 20 percent loss in productivity, but the downstream process yields were much higher than before and the overall amount of purified protein increased. This example highlights the importance of cross-functional collaboration to ensure the entire process, and not just one discrete area, is successful.

"During the process development phase, it's important that the upstream process delivers "representative" material that has a varied level of process impurities to ensure the downstream process will consistently remove these to acceptable levels. For example, a lower cell viability at harvest typically generates a greater release of host cell protein and DNA impurities. The higher impurity load can lead to diminished product recovery, or overwhelmed chromatography processes leading to a failed batch." – Ben Hughes, Director of Global Tech Transfer Biologics at Patheon.

Evaluating process variations

Collaborating to establish upstream harvest parameters is crucial to the overall downstream success, but there is also the added challenge of accommodating unexpected and unknown variations in the upstream process. Some variations can be measured, while with others the true impact may not be known until a problem emerges. When there are process challenges during purification, reviewing the following with the upstream team can help to identify the root cause of the problem:

- Has the harvest viability or titer changed?
  A change in harvest viability or titer, can disrupt the approved downstream process by fouling filters or falling outside qualified column loading ranges. Working with the upstream team to understand the expected variation and define acceptable limits will increase success. Additionally, the upstream team should immediately communicate when there are deviations in expected growth and production profiles, so that the downstream team can assess the deviation and plan accordingly.
- Were new raw materials used?
  Raw materials used in the upstream process have the potential to impact a variety of elements, including cell

growth, protein production, product quality and process impurities. As an example during the manufacturing of a recombinant protein used an animal-derived component upstream. Due to increasing regulatory requirements on animal-derived material, the team was forced to identify and qualify a new source from a different country. While in theory this was a "like for like" material change the newly sourced material resulted in an unexpected 50 percent increase in titer. Unfortunately, there was not enough capacity in the downstream process at the existing facility to handle the unforeseen increase and some material needed to be discarded. This example demonstrates that any upstream variability, even increases in titer, can be a problem when the downstream process isn't designed for it. It also highlights the importance of identifying critical raw materials, and closely monitoring any changes in lots or suppliers that could result in upstream variability.

- Is the quality profile different?
Some variability can be identified through rigorous measurements and tracking of the upstream process (e.g., titer, viability, cell growth) and some can be identified due to supply chain changes of critical raw materials. But there are other changes, that are completely unexpected, and do not become readily visible until something goes wrong downstream. Reviewing and understanding the characteristics of the product quality profiles (such as the glycosylation profile and charge distribution for antibodies) in the production bioreactor, and leveraging qualified small-scale models to troubleshoot variability during manufacturing can provide key insights when the process isn't performing as expected.

Collaborating for success

The process development teams need to openly interact with one another from the very beginning, verifying that changes made to improve or further control the upstream process will not have a negative effect downstream. The open communication and cross-pollination of ideas will also improve the coordination of project timelines and minimize material waste. Additionally, linking upstream and downstream experimental studies could provide benefits to the analytical, product characterization and formulation teams by providing them with material for their studies earlier.

Conclusion

It's important to frequently communicate and collaborate. Upstream constantly needs to be thinking about what materials they're using in their processes and what this means for downstream. Can they clear it? Will it cause interference? Variability should be minimized – a robust and consistent upstream process is key to a robust and consistent downstream process.

In short, by working together, we won't just have a successful upstream process or a successful downstream process. We can ensure that we have a robust end-to-end manufacturing process.

Serena Fries Smith is Director of Strategic Customer Engagements at Thermo Fisher Scientific, and a bioprocessing leader with over 17 years of industry experience. Hunter Malanson is Senior Field Application Specialist at Thermo Fisher Scientific, with almost 20 years of bioprocess development.

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Tax Credits: Your Work Is Worth it

Research and development tax reliefs are available for businesses in many countries, but some companies consider the area to be too complex and daunting and, in some cases, are too humble about their innovative projects.

By Peter Beavis

Many governments around the world offer corporate tax credits and other incentives for businesses – particularly those doing innovative research. The pharmaceutical industry conducts substantial R&D to develop the medicines of today and tomorrow, and the sector is in the top three in terms of intensity of innovation. However, it's not uncommon for smaller companies in the pharma field to believe that handling and understanding incentives is best left to the big fish in the industry or those with financial backgrounds. Anyone involved in manufacturing medicines and other associated products should consider R&D tax incentives as a means to help grow their business and become more competitive.

In the UK, there are three main ways that the government provides support to the pharmaceutical industry: R&D tax credits, grants and patent box schemes. Other countries also offer similar incentives. My particular specialism is R&D tax credits within the pharmaceutical sector – and it's something I'm passionate about because so many companies overlook them.

R&D tax credits are used to encourage companies to invest in innovation. This support helps bolster companies, encourage their growth and give them a competitive edge in the market. Governments want to invest in R&D because it's good for the economy; in the UK, for example, the HMRC estimated that for every £1.00 awarded to an innovative company via R&D tax credits, up to £2.35 was stimulated in additional R&D expenditure. Why? Because businesses often spend the R&D tax credit benefit they receive on funding the next big push in their R&D work, which can involve hiring new skilled staff, expanding premises, or investing in new machinery. In turn, the host country's economy benefits from the resulting increase in productivity.

In the UK, the SME R&D tax credit scheme allows companies to recoup up to £0.33 for every £1.00 spent on qualifying innovation. At £71,649, the average SME claim in pharma ranks significantly higher than the national average (£53,876). For example, if your medicines business is investing £500,000 in R&D each year, you could benefit from an R&D tax credit worth up to £166,750. And that's just the beginning – I've seen claims of much more be successful!

R&D rewards

Businesses of all sizes are typically eligible to claim R&D tax credits. In the UK, there are different types of tax relief depending on the size of the company, including a specific SME R&D relief for companies with fewer than 500 staff and either not more than €100 million turnover or €86 million gross assets. This is a pretty wide window, though SMEs will also need to consider linked companies and partnerships when working out their staff size, turnover and assets.

The most common objection I hear when talking to SMEs is: "My work doesn't qualify as R&D." The confusion is perhaps unsurprising given that the UK government's definition of R&D is found in the Department for Business, Innovation & Skills (BIS) guidelines, which are an intimidating 17 pages long. The guidelines state, "R&D takes place when a project seeks to achieve an advance in science or technology through the resolution of scientific or technological uncertainty." For some, this definition is intimidating, and for others it's plain off-putting! But it is purposefully broad because it needs to apply equally to businesses from different sectors and of different sizes.

I find there are two questions that can help companies get to the heart of R&D:

1. Are you creating a new product, process or service?

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2. Are you changing or modifying an existing product, process or service?

If the answer is yes, you should consider R&D tax credits. Essentially, if you're not sure whether your project is possible, or you don't know how to achieve it in practice, you could be resolving technological uncertainties and be carrying out qualifying R&D. And if you've taken a risk because your outcome was uncertain, this could be R&D too. Importantly, R&D doesn't have to be successful to qualify.

Pharma is full of innovation and R&D. In drug development, for example, a company may be innovating in drug delivery or formulation technologies that control a drug's release rate in the body. The development of new – or improved – coatings to prevent a drug from coming into contact with taste-buds, or the use of masking agents like flavorings and sweeteners can also qualify for tax R&D credits. The same goes for considerations relating to the shape and size of a drug, ensuring a medicine is easy to ingest and digest, while remaining effective for all patients, including children and those with disabilities. Even the non-active excipients in a product, such as binders and coatings, may require significant development to achieve the target rate of drug release and may qualify.

R&D can also encompass projects that are focused on the speed or efficiency of manufacturing. Creating an improved machinery process could qualify as R&D if, for example, it cooled something faster or used less electricity.

Innovation in pharma can also extend beyond the medicine and the processes used to make it. There is also the production of packaging; for example, precision sizing and shaping for compliance with measurement of drugs; dose-control modules for temperature control; tamper-resistant and childproof properties; security markings and anti-fraud elements to prove medicine is genuine. There's R&D in the use of eco-friendly, sustainable packaging materials and ingredients, and packaging that bonds materials together in new ways. Additives that preserve shelf life may also be eligible.

Improving IT and software is another area where medicine businesses might be able to identify R&D; for example, a new IT application that must be integrated with a legacy system. On its own, the integration process wouldn't necessarily qualify as R&D. But if the integration required some bespoke modification (usually by someone like a software developer) to overcome technological challenges, you may have the basis for a claim.

In summary, you should look at your activities and what you could potentially claim on. Don't be put off thinking that the hassle is not worth the reward! My firm was recently involved in advising a pharma company on a successful R&D credit claim to the tune of £515,000, which was based on the company's work to deduce the formulation of a drug for gout. Routine analysis was not enough to create a generic version of the medicine, and the company had to overcome the challenge of commercially synthesizing the APIs in a cost-effective and reliable way.

Too many SMEs are not making use of this valuable relief: firstly, because they don't realize they're eligible and, secondly, because they don't fully understand how much R&D credits can be worth. The power of this incentive is only realized when you start to think about how you could use the money to grow your business. Whether you want to take on more skilled professionals or invest in new equipment, the opportunities are endless. Ultimately, R&D tax credits provide cash that could spark your next big project or fund the final push in creating something remarkable.

Peter Beavis is a chemicals and materials specialist at ForrestBrown and a chartered scientist.

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SCOTTISH PRIDE AND INNOVATION

Sitting Down With…
Dave Tudor, Managing Director of the Medicines Manufacturing Innovation Centre (MMIC), Scotland, UK.

What was your first role in industry?

At university, my main focus was on organic chemistry. I loved chemistry! And I knew I wanted to use my skills to add value back to society. The pharma industry was very attractive and I was lucky enough to get job offers from Glaxo Wellcome and SmithKline Beecham. I took the latter role, but little did I know that 8 years later the two companies would merge to form GlaxoSmithKline… Ultimately, I spent 27 years at the company.

How did you rise to leadership?

As a graduate, you tend to either stay in your comfort zone or move into general leadership. I didn't have a specific career plan in mind, but when I started as a development chemist, I assumed the career that lay before me would be technical. Quite soon, however, I became a section head with a team of twelve reporting to me. Some people find leadership intimidating or stressful, but I enjoyed taking responsibility. Five years after joining the company, I moved away from synthetic chemistry to general leadership. I wanted to learn more about the company, the geographies it operated in and the different jobs throughout the business. I've never looked back!

What were your highlights at GSK?

As a young man, I visited factories and I remember thinking it would be a brilliant job to run a facility, taking responsibility for hundreds of staff, manufacturing thousands of tons of product and shipping that to patients. In 2009, I was offered a job as site director of a facility in the north east of Scotland. I loved it – it was like an extended family.

Following an amazing time as the Site Director at the Montrose facility in August, where the growth of the product portfolio and capital spend on new facilities grew significantly, I was asked to become the global supply chain leader for API manufacture. This was an amazing role and introduced me to the opportunities and challenges of running a global organization. We had facilities in Singapore, India, Australia and Europe. The job was based in London but I was able to stay in Scotland. This allowed me to get involved in wider opportunities within the life sciences sector in Scotland. I was also very involved with the Life Sciences Scotland Industry Leadership Group, and spent a lot of time with senior politicians and academics developing and executing the Life Sciences strategy for Scotland. When you get into senior management, I think it's very important to give something back to society. I'm a proud Scot and it's fantastic to give so much back to the country.

In my final role with GSK, I was Head of Manufacturing Strategy for the pharmaceutical and consumer supply chains. The diversity of the job blew me away and I loved it. I was involved if we were buying a company, selling a part of GSK, closing a factory, buying a factory… I had a great team of people and I would present senior management on a very regular basis. This also included being in charge of de-risking the supply chain from Brexit and figuring out the direction for the company.

Why did you leave?

I'd reached a high point when GSK decided to restructure. I took a redundancy package and decided it was time for chapter two, which is with Medicines Manufacturing Innovation Centre. Structurally, MMIC is run by the UK's Centre for Process Innovation, but we also have other partners, including the UK government, Scottish government, University of Strathclyde, AstraZeneca and GSK. Back at GSK before the restructuring, I actually wrote the business case for the company investing £7 million into MMIC!

I had a number of places offering me new roles, but I was drawn to MMIC. With my experience in manufacturing and strategy I thought I had a good chance of making it a success. I threw my hat into the ring – and I got the job!

What is the focus of MMIC?

The goal of MMIC is to help companies develop processes and technologies for manufacturing medicines that will help get new therapies to patients more quickly and help the sector to be more productive.

The UK is one of the most advanced countries in the world at creating new ideas, new technologies and new ways of working, but translating that capability to long-term economic growth, and getting the industry to adopt new technology or practices has been an ongoing challenge. Often, other countries were quicker at taking the technology and rolling it out elsewhere. The government was interested in how we can better translate embryonic ideas to real economic return. Meanwhile, the Scottish government had invested in innovation centers, such as the CMAC center for innovative manufacturing technologies in continuous manufacturing and advanced crystallization. The center has had significant success and is internationally recognized, and was starting to look at options to accelerate the translation of technology innovation for the industry.

A group of industry leaders thought it would be a good idea to have a Medicines Manufacturing Innovation Centre – part government owned and part industry owned – to allow for precompetitive collaboration to translate new technologies into a reality. So even before getting the role at MMIC, I was involved with the center.

What will be your priorities?

We'll be working on a number of different issues but the first two "grand challenges" will be optimization of continuous direct compression for tablet manufacture, and "just in time" automated clinical supply. These were chosen by our industry partners. The centre is in the process of being built and will be a GMP-grade pharmaceutical facility. In the meantime, we are running the development phase with 2 key partners: CMAC at Strathclyde University and the Formulation Centre within CPI. I can't wait to see the impact we'll have on the industry.

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