DECEMBER 2016 # 25

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2016 Highlights

Biopharma's Brave New Biology
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http://bit.ly/1Z47LlU

Lean, Mean Stability Machine
February 2016
Demonstrating the stability of drug formulations over a range of times and environmental conditions is essential. But what exactly should be monitored – and how often?
http://bit.ly/2gIZh4p

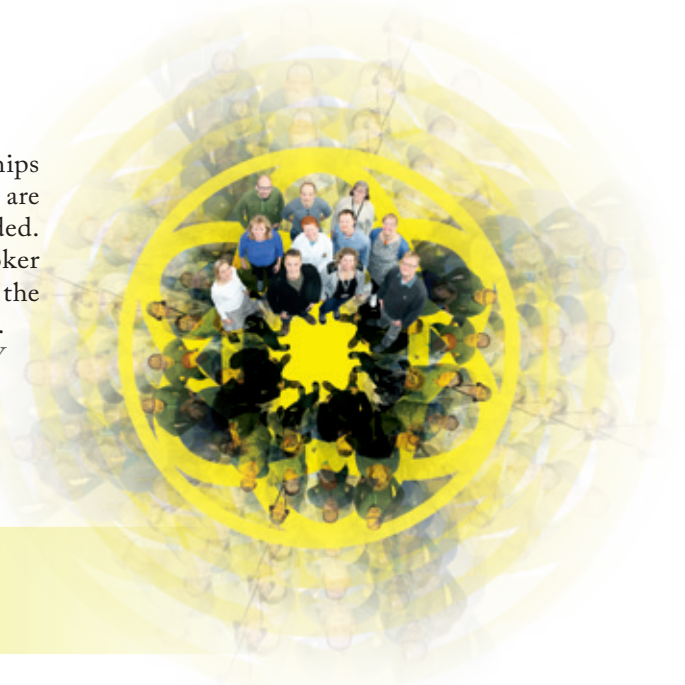
The Bright Star of Open Innovation
March 2016
In introducing an Open Innovation platform in 2015, LEO Pharma learned that if you give a little away, you can expect a great deal in return.
http://bit.ly/1pHh4M1

Finger on the Biopharma Pulse
June 2016
Experts from Ireland's National Institute for Bioprocess Research and Training – NIBRT – explain how a focus on talent, training and technology is changing the face of the biopharma field.
http://bit.ly/2axat4a

Building a QbD Masterpiece with Six Sigma
August 2016
Stuck at a Five Sigma improvement project? Or is Quality-by-Design based product development too cumbersome? Many people struggle with QbD, but there are secrets to success.
http://bit.ly/2fRk7j8

Follicular Drug Delivery: a Root to Success
September 2016
Delivering drugs through the skin without using needles has proven a significant challenge for the scientific community. Could exploiting hair follicles be the answer?
http://bit.ly/2gl1jJV

Bluff or Serious Biosimilar Bet?
October 2016
The players and chips are ready, and cards are being closely guarded. We learn what poker can teach us about the biosimilars business.
http://bit.ly/2fRkwBY



And coming up in 2017…
The Power List will be back! Nominate now at:
http://tmm.txp.to/2017/powerlist

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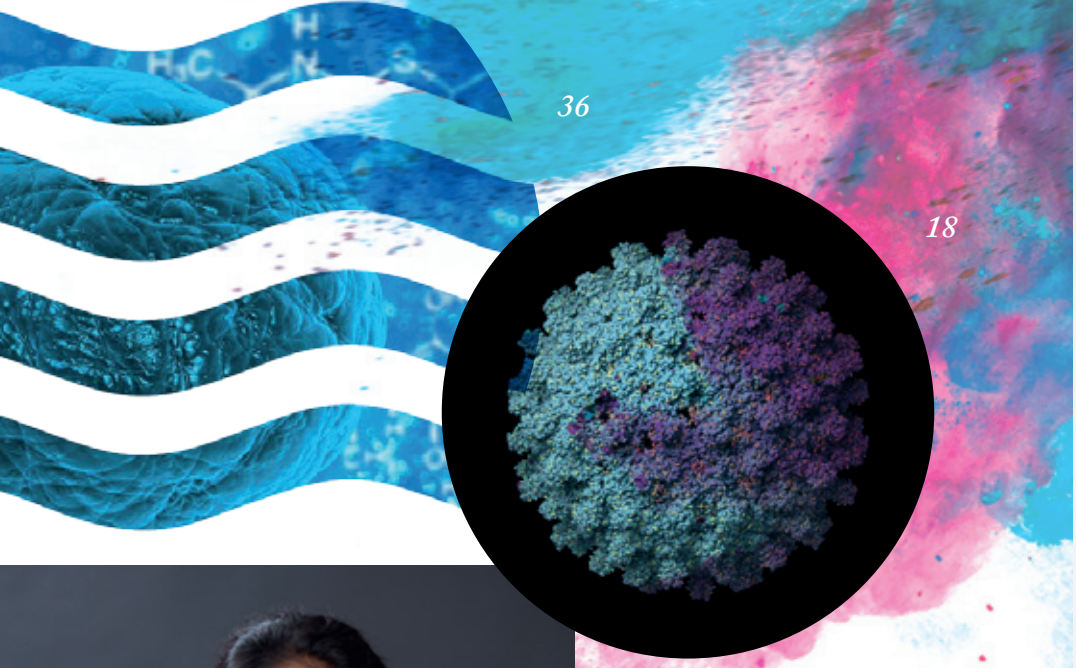

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Best Practice

Sitting Down With

the Medicine Maker

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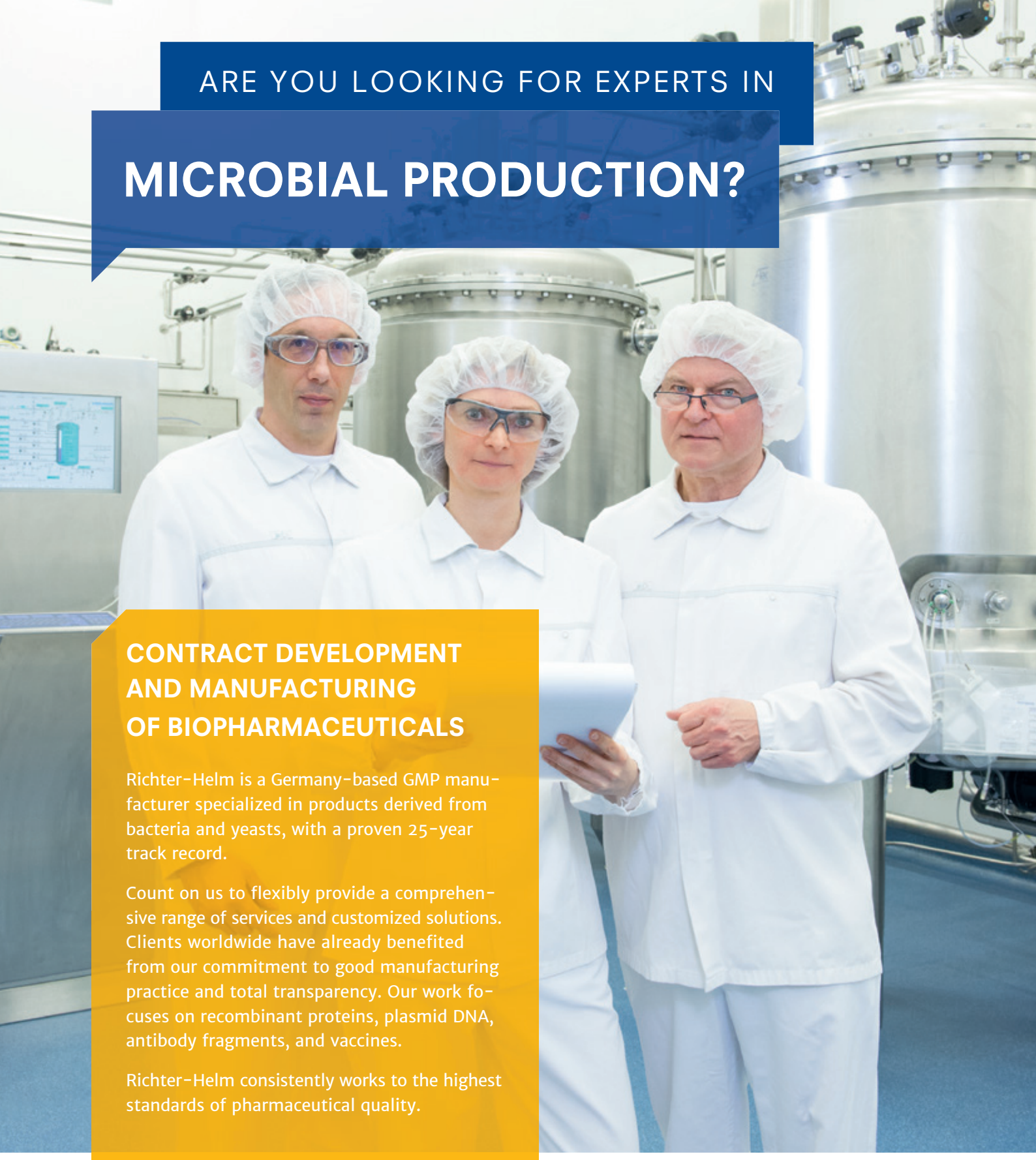

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Ending 2016 with Storms and Celebrations

A drug pricing tempest is building for 2017, but it shouldn't overshadow the great and good in the industry.

As the year comes to a close, it is a traditional to reflect on what has gone before and to look towards the New Year. 2016 has certainly given the pharma industry much to reflect on. On the business side of the industry, a storm is about to break; the long argument over the high costs of some medicines is at crunch point. Although the results of the US election initially bolstered pharma stocks, Donald Trump brought them crashing down in early December after declaring that he will bring drug prices down (1).

Meanwhile in the UK, Pfizer is already hearing the thunder after being fined £84.2 million by the UK's Competition and Markets Authority (CMA) for overcharging the National Health Service (NHS) for an anti-epilepsy drug (2). A distributor, Flynn Pharma, has also been fined £5.2 million. Pfizer sold the UK distribution rights to the drug to Flynn Pharma in 2012, which then hiked up the prices by 2600 percent. The CMA claims that the companies "deliberately exploited the opportunity offered by de-branding to hike up the price" and the UK's Department of Health is now seeking to better control high prices of generic medicines with the Health Service Medical Supplies (Costs) Bill, which is currently progressing well through UK Parliament.

Medicine cost is a subject we covered in the November issue of The Medicine Maker (3) – and you can expect more insight from the author, George Chressanthis, on this topic early in 2017.

But it's not all bad news... Looking back on articles published in The Medicine Maker, it's clear that some phenomenal advances are taking place in the industry. Some particular highlights for me include the fantastic advances in "new biology" (4), cell therapies (more about those on page 36) and bioprocessing (5), as well as the advent of novel technologies to improve manufacturing from apps (6) to augmented reality (7).

At The Medicine Maker, we like to end the year on a note of celebration. You'll find our annual Innovation Awards on page 18 – and I think you'll agree that it highlights truly ground-breaking manufacturing technologies that have been released onto the market this year alone.

It's true that the industry will face challenges in 2017, but there will be many more success stories too. I look forward to reporting on both the good and the bad. You can also look forward to more celebration in the form of our annual Power List in April 2017 – remember that nominations for this prestigious list close on February 1, 2017 (8).

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

Credit: Diana Savile, Giovanni Traverso

Star Treatment

Can star-shaped drug delivery capsules be the solution for ultra-long acting delivery?

Ultra-long acting oral dosage forms have been a goal for the pharma industry for years given that fewer repeat doses would improve patient compliance. But the developmental hurdles are manifold – the system has to stay stable in a capsule form for years, rapidly deploy in the gastric cavity, achieve multi-day gastric residence, release the drug in a linear fashion, and then exit safely out of the gastrointestinal tract. Not easy.

But Researchers at MIT and Brigham and Women's Hospital think they have mitigated these problems and developed a drug delivery system capable of safely residing in the stomach for two weeks. We asked Giovanni Traverso, senior author of the paper, and a gastroenterologist and biomedical engineer at Brigham and Women's Hospital, to tell us more.

What are benefits of ultra-long release?

The development of a capsule capable of residing in the stomach safely and releasing drug continuously enables the dosing of drugs once a week, or potentially once a month, making it easier for patients to engage with their medication. Several studies have shown that when dosed once a week rather than once a day, patients are more likely to take their medication. Our new delivery system can help address the problem of medication non-adherence, which currently costs more than $100 billion annually in the US in avoidable hospitalizations.

How does your device work?

The capsule is star-shaped and made of poly-caprolactone which is a hydrophobic polymer which protects the drug from the acidic stomach environment, and allows for gradual release over the course of 14 days. The star shape enabled extended residence due its size and the mechanical properties of the star. We focused on a drug called ivermectin, which has been used to treat parasitic infection, but also has the benefit of being toxic to malaria-carrying mosquitos. Although the system is star-shaped it is placed in a capsule and therefore what the patient swallows is identical to other capsules.

What safety concerns did you face in development?

We take safety very seriously and there were two areas of concern: potential intestinal blockage and the drug being released all at once. Regarding intestinal blockage, we have developed a system composed of linkers in the star-shaped device that selectively dissolve in the small intestines – mitigating this risk. As for the risk of releasing the equivalent of several weeks' worth of drug in one go, we designed the system to hold the drug in a solid polymer, which prevents this problem and also helps protect the drug from the acidic environment of the stomach.

You have co-founded a company to take the technology further…

That's right – the other co-founders are Robert Langer and Amy Schulman. Lyndra will focus on ultra-long acting oral delivery systems. We are targeting therapeutic areas where improved compliance and pharmacokinetic benefits can help improve patient outcome, including neuropsychiatric diseases, heart disease, and renal disease – among others. We are also working on the scale-up problem and we plan to begin first-in-human testing in 2017.

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Safe Passage for Cures

The 21st Century Cures Act is passed through US Congress – and includes big plans for the FDA

The US's 21st Century Cures Act has been in development since April 2014 – and on December 6, 2016, the Act was finally passed by the Senate in an 85-13 landslide vote. Having already passed through the House of Representatives a week earlier, the bill – which has the Obama administration's support – will become law after being rubber-stamped by the President.

In the July 2015 issue of The Medicine Maker, we discussed the potential implications of an earlier draft of the bill (1). Garrett Davis, now a former research associate at Best Practices LLC, said, "Even if just 10 percent of the current draft is implemented, it will drastically change how things work in the industry." It would appear Davis's requirement has been surpassed – with far reaching changes to the drug approval process being carried through to the final version.

Section 2061 of the bill states, "To support approval of a drug for a new indication, the FDA must evaluate the use of evidence from clinical experience (in place of evidence from clinical trials) and establish a streamlined data review program." Proponents hope this will speed up the drug development and incorporate so-called "real world evidence", such as observational studies, patient input, anecdotal data and so on, for approval of new indications for FDA-approved drugs. The Act will also allow drug companies to promote off-label uses to insurance companies, allowing them to expand their markets.

In addition, the US National Institute of Health is also set to get a substantial funding boost of $4.8 billion (although notably less than the $8.75 billion requested in an earlier version of the bill), which will help finance the Obama administration's three signature programs over the next decade: Cancer Moonshot, the BRAIN Initiative, and the Precision Medicine Initiative.

Other key features of the bill include a quicker path for breakthrough medical technologies for patients with life-threatening or irreversibly debilitating diseases, $1 billion over two years to combat the US's opioid epidemic, and $500 million dollars for the FDA to implement a whole host of new provisions.

The Cures act has gone through a number of revisions over the last two years, with two main points of contention in the Senate. The Democrats refused to approve the accelerated approval provisions unless additional funding for the FDA and the National Institutes of Health were included, while the Republicans refused to support the funding without a means of paying for it. Eventually, both sides agreed with certain compromises.

The bill, however, hasn't been passed without controversy over the new emphasis on "real world evidence". Critics of the bill have suggested that it signals a move away from clinical evidence, potentially changing the meaning of "FDA approved," which they say assures safety, efficacy and security (2). *JS*

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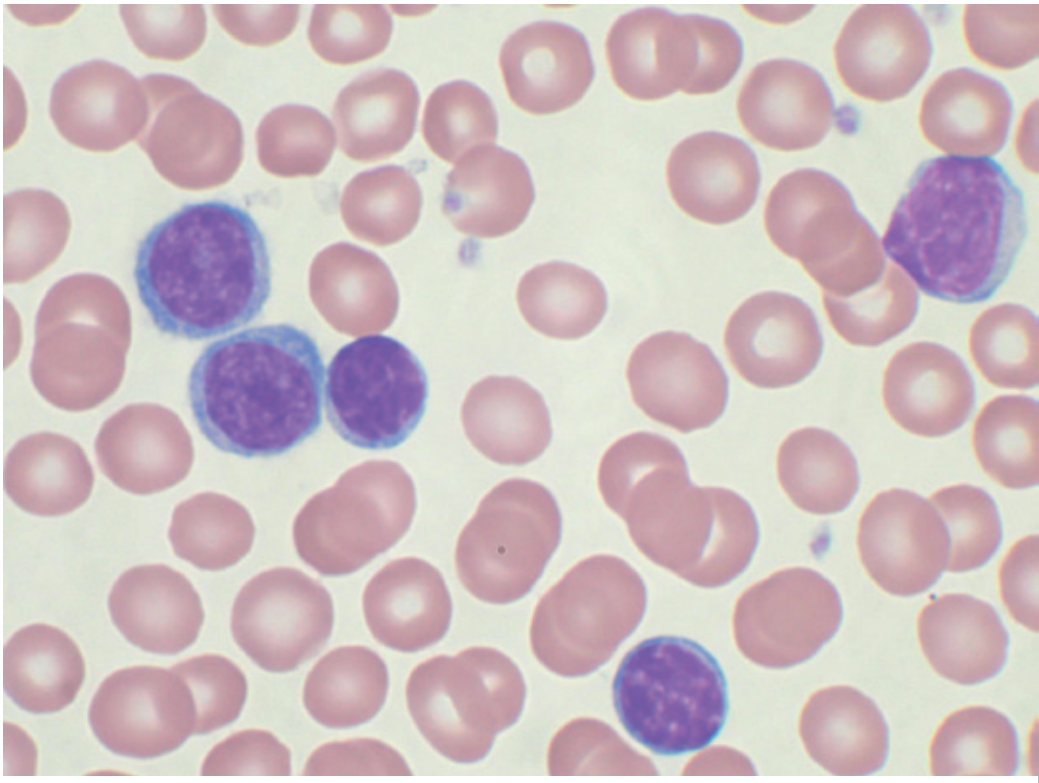
CAR-T Tragedy

More deaths in Juno's cancer immunotherapy trial raise questions over CAR-T safety, as well as FDA transparency



In July this year, Juno Therapeutics halted its cancer immunotherapy trial for after three leukemia patients – all under the age of 25 – died of a cerebral edema (swelling in the brain caused by excess fluid). The FDA cleared Juno to resume the trial only three days later, but tragedy struck again in November – with two more patients dying of cerebral edema.

The FDA's rapid decision to give the green light to Juno's phase II "ROCKET" trial of its chimeric antigen receptor T cell (CAR-T) treatment – JCAR015 – after the initial deaths, was seen as a vote of confidence in cancer immunotherapies. The FDA did not explain its motives, but a number of people within the industry have speculated that the lack of of other treatment options for the trial participants may have weighed on the decision.

Juno believed the three deaths were caused by a mid-trial modification to the protocol. After the trial was underway, Juno added a sensitizing agent, fludarabine, on the basis of promising results from the company's other immunotherapy studies. The protocol originally only included cyclophosphamide as a sensitizing agent, and it was thought that the combination of fludarabine and JCAR015 caused the deaths.

However, in light of the recent deaths it seems clear that removing fludarabine from the protocol did not solve the problem, calling into question the safety of CAR-Ts more broadly (1). For now, Juno has placed the trial on a voluntary hold: "The Company is assessing data from the cases and the trial and is evaluating its options regarding the JCAR015 program. Juno's trials and plans for its other CD19-directed CAR-T cell product candidates, including JCAR017, are not affected," (2).

The tragic events have also raised the question of clinical trials transparency and the ethics of companies being solely in charge of commenting on clinical holds or their resolution, as the FDA does not disclose their existence. "Unfortunately, because the FDA does not make its decision making process public, no one has insight into whether these issues were addressed and no one knows if the agency agreed with Juno's explanation," wrote Spencer Phillips Hay and Aaron Kesselheim in the BMJ (3).

The FDA's rapid decision was quite unusual given that holds are normally in place for months (4).

"Increased transparency related to INDs, clinical holds, and the decision making process in these and other cases could promote protection of patients to ensure a supply of volunteers for future trials, improve the experimental process for new therapies, and enhance appreciation for FDA's vital oversight role," said Hay and Kasselheim. *JS*

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The Power is Close at Hand

Nominations are open for the 2017 Power List, but will close in February 2017

The Medicine Maker is ending 2016 with a celebration of innovation on page 18. And the party is set to continue in 2017 – in April we will celebrate our annual Power List, which compiles the top 100 inspirational individuals involved in pharma manufacturing and drug development.

We have been accepting nominations for the 2017 Power List since the start of the summer, but the deadline is now close at hand. Nominations will close on February 1, 2017. To nominate, visit http://tmm.txp.to/2017/powerlist. All you need to do is tell us the person you are nominating and why you think they deserve a place on our 2017 list.

For more details, please email james.strachan@texerepublishing.com.

Number One Mystery

How solving a riddle about pungent camel urine could lead to potential diagnostics or treatments for African sleeping sickness

Sleeping sickness, also known as African trypanosomiasis, is a parasitic disease perpetuated by *Trypanosoma brucei*, and mainly affects sub-Saharan Africa – resulting in approximately 9,000 deaths a year. Researchers from Trinity College Dublin have found a new potential tool for early diagnosis – or even treatment – of the disease by solving an old riddle: why do camels infected with *T. brucei* excrete pungent red-brown urine? (1).

According to Anne McGettrick, Senior Research Fellow at Trinity College Dublin and lead author of the paper, it all started in a pub, over a pint of cold Guinness…

"Luke O'Neill, Professor of inflammation at Trinity College Dublin, had just published a paper in Nature showing that the metabolite, succinate, acted as an immune modulator," says McGettrick. "And he was chatting in the pub one evening with Derek Nolan, a molecular parasitologist at Trinity, who mentioned that *T. Brucei* produces high levels of certain metabolites in the bloodstream of infected patients – and camels."

Researchers had always thought that the metabolites were simply a by-product of their metabolism, but Nolan wondered if they might play a role in the ability of these parasites to evade the immune response. "O'Neill agreed to test some of these metabolites to see if they had any effect on the innate immune response of cells in the laboratory," says McGettrick.

The testing unearthed a metabolic by-product of *T.Brucei* activity known as indolepyruvate, which alters the composition of the camel urine – affecting its color and odor. "The advantage of the parasite excreting indolepyruvate is that it modulates the inflammatory and immune responses of the host – especially at the peaks of infection. This prolongs host survival and thereby potentiates transmission of the parasite to the tsetse fly, which ensures it can complete its life cycle," says McGettrick. "This is the first demonstration of a metabolite, produced by a parasite, interfering with the host immune response."

The researchers hope their work will open the door to new tests for early diagnosis and treatments for sleeping sickness – with indolepyruvate as a potential target. In addition, McGettrick believes the research could open up the possibility that other metabolites, produced by invading pathogens, could modulate the immune response. *JS*

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Location, Location, Location

An EMA task force prepares for the worst should the Agency be forced to leave London post-Brexit

During Britain's EU referendum campaign, many in the UK pharma industry raised concerns about what impact Brexit might have on the European Medicines Agency (EMA), currently located in London. The assumption is that EU agencies must be based within an EU member state. Indeed, a number of EU nations are already making moves to strip the UK of the Agency – Spain, Italy, Sweden and Ireland have all called for the EMA to leave London (and have made calls for the Agency to consider moving to their own countries). During an interview at Pharma Integrates in London (1), Guido Rasi, Executive Director of the EMA, raised his concerns over the disruption that relocation would cause both for the Agency and the European pharma industry as a whole.

Rasi explained that because many

EMA staff have lived and worked at the London based headquarters for over a decade, many would not wish to relocate to another European city. "I'm flattered that so many different cities and nations want us, but it would be a family decision [for the EMA staff]," he said. "We would lose quite a few very good experts."

The interviewer, Trevor Jones – visiting professor at King's College London and a former Head of R&D at Wellcome – probed Rasi on whether it might be possible for the EMA to have an official office based in the EU, but for most of the work to be carried out in London. Rasi, however, couldn't give a conclusive answer, stating, "It's beyond my power."

The location of EU agencies comes under Article 341 of the Treaty on the Functioning of the European Union, which states, "The seat of the institutions of the Union shall be determined by common accord of the governments of the Member States," (2). In other words, there's no specific treaty preventing an EU agency being situated in a non-EU country, which perhaps opens the possibility of the EMA remaining in London. But Jones argued that it seems "inconceivable" for any member state to allow the EMA headquarters to remain in London if the UK is not part of the EU.

"Where the political final decision scenario will land is very difficult to predict," Rasi explained. "I have one sure answer, which is that everybody will grant me uncertainty until the last minute."

In preparation for a potential relocation, Rasi revealed that the EMA has set up a task force. "We are preparing for all the worst case scenarios – from A to Z – including how we could cope with the loss of staff," he said. Rasi argued that over the past 20 years, the EMA has created an efficient London-based environment that would be have to be recreated, regardless of location. "We have timelines for assessments and we respect 98 percent of them," he said. "We don't want to go back." *JS*

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In My View

In this opinion section, experts from across the world share a single strongly held view or key idea.

Submissions are welcome. Articles should be short, focused, personal and passionate, and may deal with any aspect of pharmaceutical development or manufacture. They can be up to 600 words in length and written in the first person.

Contact the editor at: stephanie.sutton @texerepublishing.com

Why Share Your Biosimilars Cake?

Biosimilar drugmakers should remember that the best cake – and the best biosimilar – is one that you don't have to share with competitors.

By Guillaume Plane, Global Development and Marketing Manager, Biodevelopment Services, at Merck KGaA, Darmstadt, Germany.

With patents expiring on many established big biologic drugs, biosimilars have become increasingly tantalizing opportunities for manufacturers over the past 10 years. The first wave of biosimilars arrived in Europe in 2006 and 21 market approvals related to 14 molecules followed. Biosimilars have taken longer to emerge in North America – the first biosimilar reached the market in 2015, and only a few others have been approved since then.

Now, a second biosimilars wave – mostly related to monoclonal antibodies – is hitting, and drug makers worldwide are racing to launch these molecules. But biosimilars are not an easy business to break into and there are significant challenges. First, the manufacturer must develop a process to produce a protein that is fully comparable to the originator; second, they need to dramatically reduce the cost of goods to be the most competitive on the market; and third, they need to strategically position their products in relation to the number of potential competitor biosimilars in development.

Comparability is a key technical challenge, as the sequence of the protein is not the only attribute to consider. Many post-translational modifications, such as glycosylation, are directly related to pharmacological activity so the upstream process has to be developed with this in mind. As a consequence, analytics are a key factor of success at the very early stage of process development. Moreover, the cell line, media and feed have to be selected with attention not only to this first challenge of comparability, but also to the second challenge of cost of goods. These factors – cell line, media, and feed – directly drive productivity because of their correlation to the product's titer. And when it comes to the market, titer is ultimately the only "justice of the peace" – indeed the only leverage one has in such a competitive landscape is the price of the product, and winners are naturally those who are able to preserve margins. Paradoxically, however, post-translational modifications can be altered when the titer is increased, mainly because of overwhelmed enzymes.

These first two challenges of biosimilar development require the right skills to overcome – namely analytics, molecular biology, cellular biology and biochemistry. Bringing these skills together requires a huge effort. A number of service companies have emerged to help plug the gap for these skillsets, but there are also non-profit organizations. One non-profit initiative I would like to call out in particular is MabDesign in France, which was set up in September 2015 to help structure and support the development of therapeutic antibodies and immunotherapies in France. The company already has over 80 members, including immunotherapy developers, service providers, training organizations and equipment suppliers. Biopharma development is becoming ever more complex so collaboration is key. MabDesign has been developing specialized training solutions and setting up scientific events (both regional and international) to help promote networking and innovation.

Of course, in addition to the right skills, the right equipment is also key. Fortunately, vendors are continuously improving their systems and developing new end-to-end solutions. For manufacturers, using the newest and most efficient technologies can provide benefits in terms of cost savings during manufacture.

And what about the problem posed by the vicious competition in the marketplace? Today, almost four hundred biosimilar drugs are under preclinical or clinical development in the world, competing with fifty originators. These development programs are not equally distributed among originators, and the current trends show some opportunities for strategic positioning. It is interesting to note that some originator biologics (trastuzumab, bevacizumab, adalimumab) are currently challenged by more than thirty biosimilar programs – one (rituximab) is faced with more than forty programs. All of these programs are clearly appetized by the topline revenues of the originator biologic – between $6 billion and $8 billion for each – but it seems that many biosimilar drug makers have forgotten that they may only end up with a very thin slice of cake... All of these manufacturers will only have one main point of leverage to be successful once marketed: adapting the product price to the competitive landscape. When considering the cost of biosimilar development (around $80-200 million), the reality of having to share your cake with dozens of competitors must also be considered.

In contrast, other originator biologics, although less attractive from a revenue standpoint, may offer better outlooks for biosimilar drug makers because few competing products are in development. In my view, eculizumab is without question the best example: this originator generates $2.2 billion in revenue, its patent will expire in 2020, and only one drug maker is developing a biosimilar product so far. No doubt that this drug maker has selected a fine cake, and has a more significant chance at success than the developers of rituximab or trastuzumab biosimilars. Time will tell how successful this audacious positioning turns out to be.

Finding a Fumigant

Formaldehyde's days as a fumigant are numbered, but choosing an alternative isn't easy. Here are some things to consider...

By Andrew Ramage, Microbiology Product Specialist, Cherwell Laboratories, UK.

Looking back at my time as a laboratory-based microbiologist, I spent most of my career using formaldehyde to fumigate microbiological safety cabinets, high containment level areas and cleanrooms. I performed my first fumigation of a microbiological safety cabinet in 1999 and even then there was talk of formaldehyde being banned for use as a fumigant. It has been suspected for many years that formaldehyde is carcinogenic, so why it has taken so long to be classified as such is a mystery. It is only now, thanks to a combination of REACH regulations and the Biocidal Products Regulation, that its days of use in the EU as a fumigant in "public areas" are numbered. That decision is due imminently and may already have been announced when this article is published...

Many companies have long since moved away from formaldehyde, but others have stuck with it for a number of reasons – cost, of course, is one of these, but so too is the time and resources required to research, trial and validate a new system. Time is money and revalidating a whole site or facility means a lot of down-time. Had I stayed in my previous post, attempting to arrange the time to revalidate those labs with the area managers would have been a total nightmare – and the inconvenience of a lengthy shutdown for them would have been close to intolerable. Two of the alternative chemicals, peracetic acid and chlorine dioxide, both produce highly toxic and possibly corrosive chemicals when they react with formaldehyde. Formaldehyde can linger in HEPA filters for many months post fumigation, so they need to be replaced even before a trial, let alone a validation, which increases the expense significantly.

The reason to move away from formaldehyde is ultimately a health and safety one, so what should companies still using formaldehyde turn to now? Larry Joslyn describes the ideal fumigant as one that should leave no residues, or that can be rapidly removed to safe levels following fumigation (1). There are plenty of systems available that claim 'no residue' and 'rapid removal' post fumigation. Each manufacturer or distributor provides – as part of the product literature – papers written in conjunction with customers claiming to prove the effectiveness of their system. As a customer, I would be a little skeptical; few (if any) manufacturers will publish data that suggest their system is not effective. For me, there are too few independent comparison studies of fumigation systems. So many 'studies' seem to come from a distinct angle:

extolling the virtues of a favored system. Which one are you going to believe? That was always my conundrum when seeking systems to replace formaldehyde.

The choice of chemical was of greatest importance. It has to show the desired efficacy against the microorganisms handled in those laboratories. In a facility handling pathogens, the chemical chosen has to be effective against the most resilient pathogen the facility handles in the event of a spillage of a high-titer culture. Regarding the efficacy of these fumigation systems in that scenario, there are few papers available that use simulated spills – and most studies take place in pristine cleanrooms where there are few variables to affect the results. Using a substitute organism to replicate a spill puts the operator and the room it is being performed in at risk, so those studies are few and far between.

I would say that choosing a fumigation system in a facility that doesn't handle pathogens is considerably easier than one that does, based on the requirement of efficacy against particular pathogens. However, here is another factor that may muddy the water: I've heard some say that the existing standard of achieving a 10,000,000 kill of spores is too harsh, partly because cleanrooms don't have that spore level. In addition, there is a danger of false positives because of the way biological indicators are made. Personally, I can't see the regulators changing those regulations, as the worst-case scenario must always be considered.

If I had to choose a new fumigation system, my feeling is that there is a lack of independent data out there giving a more transparent comparison of fumigation methods. Whatever system you choose I hope that it is appropriate for your needs and ultimately works to your specifications.

Finding Fakes

Looking at the past, present and future of counterfeit drugs screening.

By Ravi Kalyanaraman, Ph.D., Associate Director at Bristol Myers Squibb and Varsha Ganesh, M.S., Associate Scientist at Bristol Myers Squibb, New Brunswick, New Jersey.

Produced and sold with the intent to deceptively represent origin, authenticity or effectiveness, counterfeit drugs are products that contain no active ingredient, inappropriate quantities of active ingredients or other ingredients that are not found in the genuine product. Estimates suggest that the global counterfeit drug market sits somewhere between $75 and $200 billion and represents 10 – 50 percent of all drugs sold in some low-income countries (1).

The first step in authentication testing is to compare the packaging and drug product appearance of the 'suspicious' product with the genuine product. However, physical appearance is easily counterfeited, so robust chemical analysis must be used to distinguish between authentic and fake drugs. Needless to say, analytical testing must be both accurate and rapid in this setting.

Traditionally, qualitative and semi-quantitative techniques – for example, disintegration, colorimetry, and thin layer chromatography (TLC) – have been employed to determine if a product is counterfeit (2). Notably, these techniques have been especially useful with regards to taking the 'lab' to the field, providing a simple and inexpensive way of determining counterfeits. Global Pharma Health Fund (GPHF)- Minilab still supplies field test kits with simple disintegration, color reaction tests and easy-to-use TLC tests for rapid drug detection and drug potency verification (3).

When it comes to a detailed characterization of counterfeit drugs, gas and liquid chromatographic techniques (GC and LC) are the most prevalent (4). Coupling mass spectrometry (MS) to LC not only assists in authentication but identifies even low concentration of substitute ingredients in a counterfeit. The drawback with such methods is the sample preparation and high lead time required for analysis. To overcome this, direct-ionization MS methods, such as direct analysis in real time (DART) and desorption electrospray ionization (DESI) are being used to eliminate sample preparation (5).

Spectroscopic techniques, such as benchtop FT-Raman and near-infrared spectroscopy (NIRS) possess a distinct advantage over chromatographic techniques in that they are non-destructive and can rapidly characterize the suspect product in seconds – even without the need to remove the drug from its packaging (6). Such portable spectrometers offer a rapid, accurate and specific means of authentication in-field, as they are able to compare the unique spectral signatures or 'fingerprints' of the authentic drug product against the suspect. Furthermore, they require little to no training, which means they can be used in the field by law enforcement officials, ensuring immediate identification and take down of counterfeit activities (7).

But what about the surge in the number of protein-based drugs on the market? The extraordinarily high costs associated with biologics make them a lucrative market for counterfeiters – as proved by the recent case of counterfeit Avastin (8). Biologics are, of

course, large complex molecules, which makes them hard to characterize and fingerprint. We were part of a team at BMS that was able to show that confocal Raman spectroscopy – coupled with a specialized sample preparation technique called drop coat deposition (DCD) – can be effectively used to fingerprint biopharmaceuticals (9). The technique, coupled with peak fitting, could also be used to determine the secondary structure of the biologics and even offer a way to distinguish between biologics and their generic versions (biosimilars). DCD Raman (DCDR) spectroscopy requires limited sample preparation (deposition of a microliter 'drop' of sample followed by solvent evaporation) and yet offers a wealth of structural information (secondary structure can be classified using the Amide I band).

Analytical technology for counterfeit detection has certainly experienced tremendous growth and evolution over time. However, as counterfeiters get smarter and move into the biopharma space, we must arm ourselves with superior authentication techniques. In our view, DCDR spectroscopy is one such tool.

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the Medicine Maker *Innovation Awards* 2016

Innovation Returns

The Medicine Maker Innovation Awards are back for the second year to recognize the most exciting drug development and manufacturing technologies released during 2016.

Innovation is crucial in any industry, but its impact is perhaps best felt in the pharma, medical and healthcare fields where it saves lives. Ground-breaking new drugs for unmet needs or scientific advances that open the way to new treatment options probably spring to mind first – but let's not forget the technologies, tools and services that are essential along the way.

2015 marked the birth of The Medicine Maker Innovation Awards, which showcase the most impressive launches over the year. Based on collated comments and rankings from an anonymous judging panel, we presented the Top 10 innovations in our first Innovation Awards – with LEO Pharma's Open innovation platform taking the coveted top spot (read an update on page 26). For 2016, we've decided to crank things up a notch, given the tremendous number of nominations received – many of which caught the eyes of the judges. Here, we present the Top 15 innovations of 2016. Which stars shone the brightest in 2016? Our team of anonymous judges have made their decisions – but do you agree? We welcome your views.

15

FEC40 CAPSULE FILLER

A capsule filler with an output of up to 400,000 capsules per hour

Produced by Fette Compacting

The FEC40 is a compact system for hard capsule filling that uses a patented dual capsule filling process to help boost output to up to 400,000 capsules per hour, without needing to increase the machine cycle time. The capsule filler was developed using the same principles of the company's double rotary tablet presses. Fette has merged traditionally separate process steps for capsule filling and used the resulting free space for dual arrangement of capsule filling, resulting in an output almost double that of many other machines.

Potential impact:
Capsules are second only to tablets in terms of dosage forms for pharmaceuticals and nutritional supplements. Today, more than 400 billion hard gelatin capsules are produced worldwide every year. Despite these large numbers, Fette says that the output volume of machines used to date is usually around 250,000 capsules per hour.

What the judges say:

"This is a huge output for a capsule filling machine."

TOYOPEARL SULFATE-650F

14

An ion exchange chromatography resin that binds proteins under atypical conditions

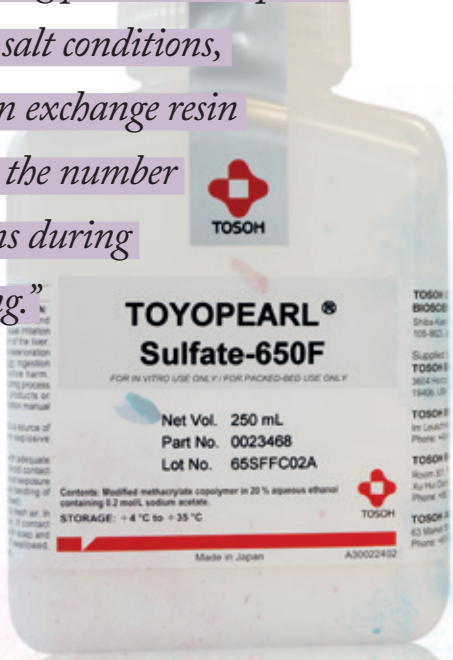
Produced by Tosoh Bioscience GmbH

In contrast to many common ion exchange resins, the presence of salt ions can be tolerated during protein adsorption when using TOYOPEARL Sulfate-650F. TOYOPEARL Sulfate-650F is a strong cation exchange resin that exhibits high salt tolerance, while allowing for high-protein binding capacities across a wide range of pH values and conductivities. According to the company, the resin is especially suitable for the purification of therapeutic antibodies.

Potential impact:
Current purification processes frequently require diafiltration or dilution steps before loading the target onto the first ion exchange column. Protein purification with Tosoh Bioscience's new resin can help potentially shorten and simplify the whole process as physiological salt concentrations can be tolerated during protein binding.

What the judges say:

"By permitting protein adsorption under high salt conditions, this new ion exchange resin may reduce the number of operations during bioprocessing."



SYRINA AR 2.25 AUTO-INJECTOR

A fully automatic autoinjector for the self-administration of viscous drug formulations

13

Produced by Bespak Europe

Bespak says that delivering drugs quickly can be a problem for spring-based auto-injectors, especially for viscous formulations. Syrina AR 2.25 is an auto-injector that has been designed specifically for delivering larger volume viscous drug formulations. The device can be used by patients to self-administer their medication and is fully automatic. Based on VapourSoft inhaler valve technology, the autoinjector uses a miniature canister of liquefied HFA gas as its power source to deliver difficult-to-administer formulations in a controlled manner.

Potential impact:
Biologic drugs form an increasing proportion of pharmaceutical pipelines and sales, and most of these will need to be delivered by injection. There is also a drive towards improved patient convenience and a focus on minimizing administration frequency. Syrina AR 2.25ml is a drug delivery device that can do this safely and smoothly.

What the judges say:

"Auto-injectors are a big focus for companies, but this one stands out in being designed specifically for viscous formulations."

PERFEXION

A production quality process to control and monitor glass tubing

12

Produced by Schott AG

When it comes to pharmaceutical primary packaging such as vials, cartridges or syringes, fluctuations in tubing dimensions can have a significant impact on the container performance. Traditionally, manufacturers of glass tubing have monitored quality parameters on a random sample base, but Schott believes there is a better solution. The company has developed a new production quality process. PerfeXion allows for more accurate monitoring – and closer control of – the glass tubing later converted into primary packaging containers. Various interacting online inspection devices, in combination with integrated data collection and data analysis, allow all relevant quality parameters of the original tube to be ideally adapted to the container format (syringe, cartridge, vial or ampoule) and customer specifications.

What the judges say:

"The quality of syringes and other primary drug packaging is crucial – this process could help prevent some of the quality problems associated with glass, which are too often seen in industry."

Potential impact:
PerfeXion is a way of setting the foundation for subsequent steps in the production of pharmaceutical packaging containers. The process targets quality requirements and allows for a customization of specific parameters. Fluctuations in critical glass tubing dimensions can be reduced, which Schott believes will lead to a more constant gliding force of syringe plungers and higher dosage accuracy of multidose cartridges.

Q EXACTIVE BIOPHARMA

Three optimized workflows for comprehensive biopharmaceutical characterization in a single platform

Produced by Thermo Fisher Scientific

Thermo Fisher Scientific says that the Q Exactive BioPharma MS/MS Hybrid Quadropole-Orbitrap mass spectrometer takes advantage of the high-resolution, accurate-mass (HRAM) capabilities of the company's popular Orbitrap mass analyzer to enable three key protein characterization workflows: denatured and native MS intact analysis, subunit and top/middle-down analysis, and peptide mapping. The system also features a high mass range mode that adds the ability for intact monoclonal antibody and antibody-drug conjugate analysis, under both native intact and denatured intact conditions, to the existing capabilities for subunit top/middle-down and peptide mapping analysis.

Potential impact:
Researchers require multiple mass spectrometry techniques to perform experiments around biopharmaceutical structure characterization. This system brings a number of Thermo Scientific technologies together into one system that can be used to analyze antibody-based biologics at the intact, subunit, and peptide levels.

What the judges say:

"This system provides a very broad range of high-quality data for protein characterization and addresses critical needs of biologics manufacture."

GOLDEN NUMBER

Universal identifier to help identify persons and facilities involved in clinical research

Produced by DrugDev

Study planning and site identification for clinical trials, according to DrugDev, is not easy. There's plenty of data out there, but there isn't a common data model, or a unique identifier needed to link the sources of information resulting in non-enrolling or under enrolling sites, which adds cost and time to the clinical research process. DrugDev has created a data model with standard terminology, lists of values, and a universal identifier for investigators and sites called the Golden Number that allows individual pharma companies and CROs to match and share data across collaborations.

Potential impact:
The lack of a common identifier can result in sub-optimal decisions for study planning, feasibility and site selection. It also can create significant business process inefficiencies in in areas such as data integration and consolidated financial reporting. DrugDev believe that the Golden Number can help reduce the number of non-performing sites, decrease the need for rescue sites, reduce IT time and cost spent on data masters, and improve site engagement.

What the judges say:

"DrugDev are drawing attention to a complex problem that deserves greater recognition and more solutions."

09

OPADRY QX

A flexible film coating that can be applied across a broad range of process conditions

Produced by Colorcon

Opadry QX is a film coating system suitable for fast application that is scalable across a range of coating equipment and process conditions. The formulation – based on high solids and low viscosity ingredients – reduces preparation and production time, which increases coating process efficiency and helps reduce costs across all types of equipment, according to the company. Opadry QX also enables the coating of temperature-sensitive active pharmaceutical ingredients.

Potential impact:
Drug makers are always looking for ways to make their manufacturing processes more efficient – particularly with the trend towards continuous processing. Opadry QX is flexible enough to be applied at a range of solids concentrations (20-35 percent), which make it well suited for continuous processing. Moreover, because Opadry QX works well in all equipment types and is robust across a wide range of process airflows and temperatures, it can be used in the different coating equipment types found around the world.

What the judges say:

"A very flexible coating that can ease manufacturing."

08

VCAPS ENTERIC CAPSULES

Enteric Capsules that provide enteric release drug delivery without the need for a functional coating

Produced by Capsugel

Capsugel has developed a line of functional capsules that provide intrinsic enteric protection and delayed release without the need for a separate functional (enteric) coating. Pharmaceutically approved cellulosic enteric polymers are incorporated into the capsule shell and the capsules are produced using the conventional pin-dipping capsule manufacturing processes.

Potential impact:
By eliminating the need for enteric coating, Capsugel says that the intrinsically enteric capsules can accelerate preclinical assessments and clinical development for compounds requiring enteric protection and/or delayed release in the upper gastro-intestinal tract. The capsules can also enable the oral delivery of small and large molecules that require enteric protection, but are usually degraded by the heat associated with coating processes.

What the judges say:

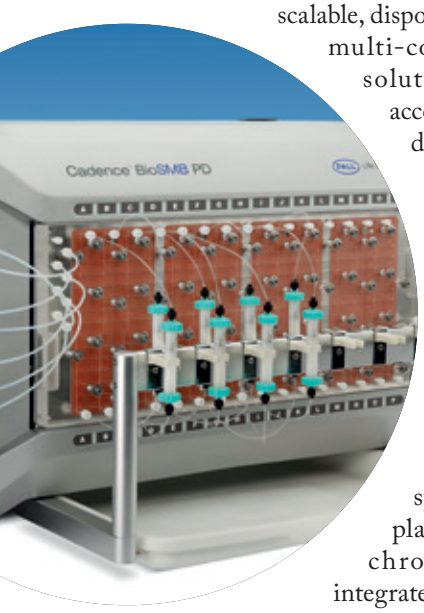
"Could potentially enable more rapid and convenient enteric formulation of a broad range of thermosensitive drugs."

CADENCE BIOSMB

07

Multi-column chromatography system for purification processes up to 2000L

Produced by Pall Life Sciences



The Cadence BioSMB process system is a fully scalable, disposable flow path, continuous multi-column chromatography solution – a market first, according to the company. It is designed for easy conversion from an existing process development-scale continuous purification step into a GMP-process scale continuous purification based on feedstreams derived from fed batch bioreactors of up to 2000L. The system features an open platform with eight smaller chromatography columns, integrated single-use pump heads, a valve cassette, sensors and flow path.

Potential impact:
The open platform of the BioSMB process system allows for the use of multiple chromatographic technologies, as well as more efficient use of chromatographic sorbents resulting in smaller column volumes and improved process economics. The eight columns provide flexibility and control, while delivering reductions in chromatographic media use (up to 80 percent). Additionally, the single-use flow path can be replaced in 30 minutes, and the valve system does not require cleaning or validation.

What the judges say:

"This could contribute to increasing the efficiency and decreasing the costs of biologics manufacture."

06

CSP ACTIV-BLISTER SOLUTIONS

A packaging solution to control the internal atmosphere of existing individual blister cavities

Produced by CSP Technologies

Activ-Blister protects moisture- and oxygen-sensitive solid dose pharmaceuticals packaged on thermoform-fill-seal and fill-seal equipment. It helps to control the internal atmosphere of existing individual blister cavities by offering moisture, oxygen and combination absorption without the use of adhesives and without changes to the existing footprint of a packaging line. The technology can be incorporated into a wide range of blister packaging formats, including push-through, peel/push, and high barrier foils, including both coldform and thermoform.

Potential impact:
This technology enables pharmaceutical manufacturers and contract packagers to achieve moisture protection without using coldform foils, which can be expensive. It also allows for a smaller blister footprint (around 40 to 60 percent size reduction), and provides clear visibility of the tablet/capsule in the blister cavity. Products normally packaged in bottles with desiccant sachets can now be thermoformed into blister cards, eliminating the added costs associated with gas flush/purge and secondary packaging with sachets.

What the judges say:

"As well as being compatible with a broad range of legacy systems, this packaging has the potential to help reduce costs while increasing stability and shelf life."

OPTIFORM SOLUTION SUITE AND OPTIFORM SOLUTION SUITE BIO

Accelerated parallel screening platforms that help match early phase small and large molecules with the best formulation options

Produced by Catalent

OptiForm Solutions Suite and OptiForm Solutions Suite Bio address bioavailability and delivery challenges for both small and macromolecules respectively. OptiForm Solutions Suite employs molecule characterization and five formulation technologies – particle size reduction, lipid formulation, salt form optimization, and solid dispersion, including hot melt extrusion and spray dry dispersion. The platform matches the best formulation technologies to the molecule using accelerated parallel screening – within twelve weeks. OptiForm Solutions Suite Bio is a screening technique specifically for the assessment of oral macromolecule delivery.

What the judges say:

"Being able to bring more oral biologics to market would be a big win for the patient community."

Potential impact:
According to the company, around 70 percent of molecules in development suffer poor oral bioavailability. These platforms can help quickly and efficiently identify the most suitable formulation technology and achieve optimal bioavailability for advancement into animal pharmacokinetic studies and future development. For macromolecules, oral delivery may help patient acceptance and compliance versus injection and reach optimal clinical outcome. OptiForm solutions Suite Bio can rapidly screen biomolecules' potential for oral delivery. By quickly evaluating all best available technologies, innovators could improve R&D productivity and lower costs by rapidly progressing difficult molecules.

CADENCE ACOUSTIC SEPARATOR

A technology for continuous clarification of batch cell culture

Produced by Pall Life Sciences

The technology makes use of acoustic forces to enable the continuous removal of cells and cell debris through the Cadence single-use acoustic chamber – achieving clarification of harvested cell culture fluid for downstream processing. Acoustic forces are applied across a counter-current flow of bioprocess fluid to generate three-dimensional standing waves that trap cells at their nodes. This leads to aggregation and precipitation from suspension, preparing the cells for simple extraction. According to the company, the Cadence Acoustic Separator (CAS) results are very reproducible.

Potential impact:
The system can clarify many types of biologic products, including recombinant therapeutic proteins and mAbs, regardless of variability in particulate concentrations and cell culture density, turbidity and viability. According to the company, CAS enables up to 75 percent reduction of the filtration area and associated buffer volume requirements, leading to cost savings and reduced tank sizes. Additionally, the CAS can be integrated into both semi-continuous and fully-continuous bioprocesses.

What the judges say:

"Its broad applicability, compatibility with continuous processing and potential for savings in terms of buffer use and space requirements make this of wide interest."

WORDS OF A WINNER

The winner of The Medicine Maker 2015 Innovation Awards was LEO Pharma's Open Innovation platform (http://openinnovation.leo-pharma.com). Under the free-to-use research platform, launched in March 2015, researchers can submit their compounds to LEO Pharma for testing with propriety assays for psoriasis and eczema. You can read the full story behind the platform on The Medicine Maker website (http://bit.ly/1pHh4M1). One year on from winning our inaugural Innovation Awards, we caught up with Niclas Nilsson, Head of R&D Open Innovation at LEO Pharma, for an update on how the scientific community is responding to the platform.

What's the latest with the platform?
We've done some tweaking to the platform – mainly the contractual details – but it's now well established in our research organization. As of October 2016, we have engaged with 23 biotech companies and 10 universities. For a medium-sized pharmaceutical company, I think this is excellent progress – and it has created many external opportunities.

We really appreciate all of our partners who have engaged with us and submitted their molecules, and we regret that we have to send a lot of negative results back! Even negative results, however, can provide valuable scientific and strategic feedback and I think that the platform is a valuable matchmaking opportunity to find external partners.

What success stories can you share?
As a direct result of the scientific data generated by the platform, we have identified a few external partners with whom we are following up with more specific activities. In one example, two new targets that are involved in advanced in vitro disease models have been identified – targets that we didn't even know existed! It is unclear how this eventually will translate to patients, but that's a general problem we always face in drug research.

In a second example, we received new chemistry that will jointly allow us to better evaluate the relevance of a previously known, but inaccessible target (because of a functional tool compounds and chemistry for biological experimentation).

In both cases, we now have the opportunity to expand our early drug research pipeline and disease understanding. The external partner benefits by increasing the value of their assets, as well as having the opportunity to help advance their technology further.

What about future developments?
We are very excited about open innovation and currently looking at how we can expand the scope and use of our platform. For example, we would like to provide a platform that works as an open source community, allowing all potential partners to interact and exchange needs and opportunities. The details behind this are being considered. If all goes well, we will probably see a step-by-step introduction, starting with a rework of the web portal in early 2017.

Given that the current platform is very well geared towards

identifying new molecular pipeline opportunities, we would also like to enable collaborative research, with the aim of progressing disease understanding on a biological level. For this purpose, the platform will also need to address cellular targets and disease pathways. This is something we can do today using tool compounds and chemical probes, but we would like to strengthen this together with academic researchers.

Furthermore, we would like to be able to provide testing of modalities other than small molecules by perhaps opening up for external suppliers of, for example, antibodies, peptides and larger molecules – and perhaps even genes, cells and other completely new technologies that could become tomorrow's solutions to today's unmet medical needs.

03

What the judges say:

"The Vanquish UHPLC platform is well used and appreciated by industry – this latest system now adds the option for binary solvent delivery."

"Innovations in UHPLC are making the technology increasingly accessible and easier to use."

VANQUISH FLEX BINARY UHPLC

Fully biocompatible ultra-high performance liquid chromatography system with high throughput capabilities

Produced by Thermo Fisher Scientific

The Vanquish Flex Binary UHPLC (ultra-high performance liquid chromatography) system is a new addition to Thermo Scientific's Vanquish UHPLC platform that adds a binary solvent delivery option in the 1000 bar (15,000 psi) performance range. The system has been designed for high-speed, fast gradient applications, and features a binary high-pressure gradient pump with 2 x 3 solvent channels and low gradient delay volume that can deliver high flow rates of up to 8 mL/min. In addition, the system features intelligent sample pre-compression, multiple modes of thermostatting and allows for broad flow rates and temperature ranges.

Potential impact:
Thermo Scientific believes that their system gives analysts the "separation power" to identify very low levels of impurities/metabolites in challenging matrices and to uncover minor post-translational modifications. In addition, the use of a high pressure limit and advanced pump technology could help permit rapid sample turnaround and decision making.

SMARTDOSE

Wearable, integrated drug delivery device for sensitive drug products

Produced by West Pharmaceutical Services

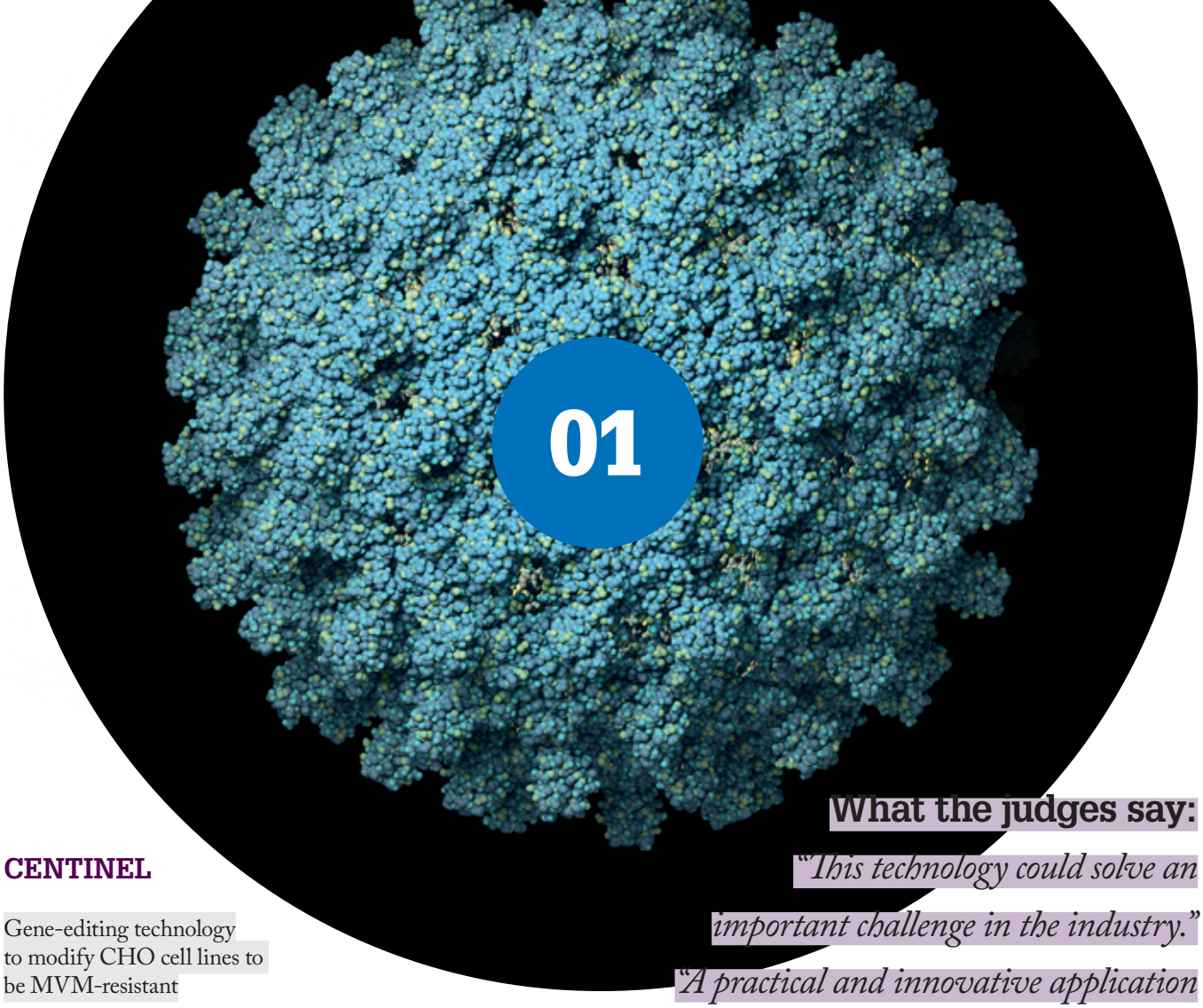
The SmartDose platform is a single-use, electronic wearable injector that allows patients to self-administer medication. The device is discreet and placed on the body – usually the abdomen – and has been designed with human factors testing to minimize discomfort. It incorporates a polymer-based drug container (made from Daikyo Crystal Zenith cyclic olefin polymer) with a drug delivery system that can be pre-programmed to deliver high volumes of sensitive drug products. The company says it is particularly well matched for high-viscosity and silicone-sensitive biologic formulations.

Potential impact:
The technology is designed to enable effective delivery of injectable biologics, which can present several challenges for drug packaging and delivery. Many biologics are sensitive, creating potential for interaction with containers and packaging components. Additionally, biologics may require large doses to be injected slowly over time. West believes that the design of the SmartDose platform enables safe, effective and accurate delivery of biologics, while helping to improve the patient experience.

What the judges say:

"Self-administration of biologicals is an important and growing field; systems such as this, which both improve the patient experience and address some of the difficulties of biologics delivery, will no doubt be welcomed by patients."

"A wearable drug delivery device is highly innovative – and a great leap forward for the field."



01

CENTINEL

Gene-editing technology to modify CHO cell lines to be MVM-resistant

Produced by Merck KGaA

Merck KGaA's Centinel is a gene-editing technology that can be used to modify CHO cell lines to create resistance to minute virus of mice (MVM) – a contamination threat in biopharma manufacturing. The company says the technology was developed after Merck KGaG identified a gene target (Slc35a1) which, upon elimination of expression by gene editing, resulted in a CHO cell line resistant to MVM – while still retaining an equivalent level of protein quality and cell line productivity.

Potential impact:

For biopharma manufacturers using CHO cells, contamination by a small, non-enveloped parvovirus called minute virus of mice (MVM) is a significant threat. To date, most MVM risk mitigation efforts have focused on raw material qualification, viral filtration and inactivation techniques. One of the main challenges with media and cell culture MVM contamination, however, is that it typically eludes detection until the virus has had a chance to infect a cell and multiply. The first signs of contamination may include a drop in viable cell count or a decrease in recombinant protein production. Although infrequent, infection of a fermenter can be catastrophic for a producer, resulting in the loss of product, temporary withdrawal from the market and extensive clean down costs.

Given that CHO-based animal component free (ACF) systems are currently responsible for producing billions of dollars' worth of therapeutic products every year, adding MVM resistance to a CHO bioproduction cell line could provide an added layer of defense against virus-induced catastrophic failure in animal-component free fermentation systems.

What the judges say:

"This technology could solve an important challenge in the industry."

"A practical and innovative application of gene-editing technology to enhance biomanufacturing."

"MVM is a significant problem in biopharma manufacturing that creeps up again and again – and is hard to detect before it's too late."

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Facility Innovation by Design

What do ISPE's 2016 Facility of the Year Awards tell us about the future direction of the industry?

By Stephanie Sutton

The pharma industry changes slowly – it's the inherent nature of the beast given tight regulations and the fact that drug development timelines can be well in excess of 10 years. In addition, pharma still depends on a tremendous amount of stainless steel infrastructure. Facilities can take years to plan, design and build – and sometimes, by the time they are ready to be used, they are already out of date. Pharma is well aware of the danger and is working hard to develop facilities that are not only fit for the present, but also a future that will demand higher quality at lower cost, as well as taking into account the uncertainty of competition from new therapeutic areas, such as cell and gene therapies.

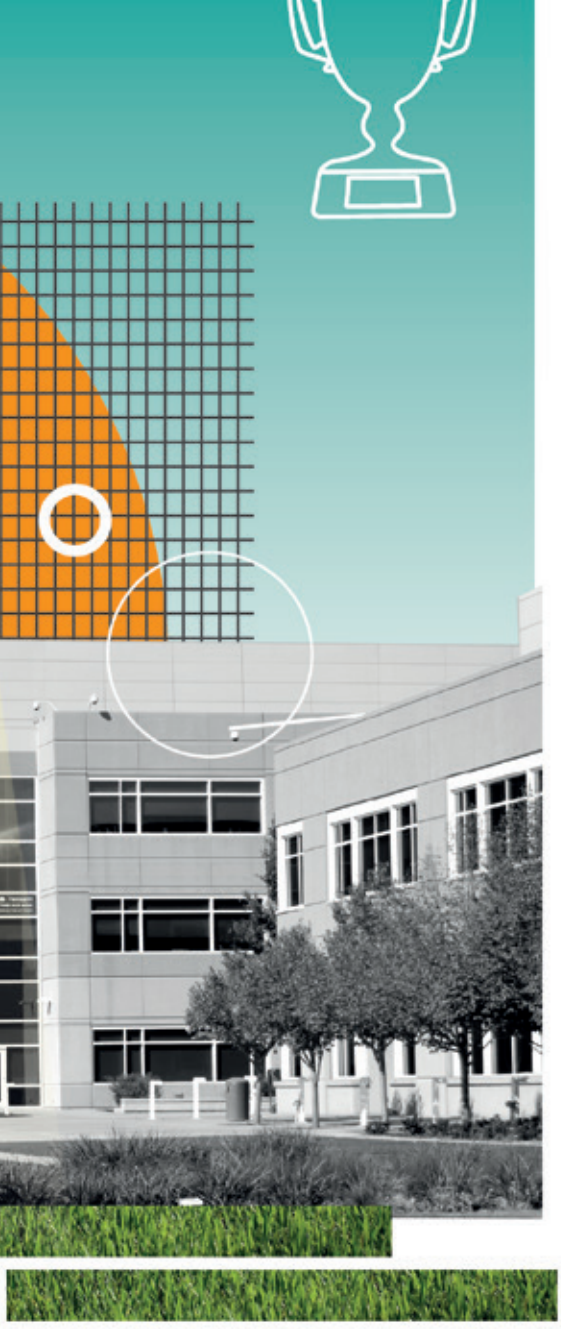
The International Society for Pharmaceutical Engineering's (ISPE) Facility of the Year Awards (FOYA) aim to bring the importance of facility design into the spotlight – and to showcase the successes so that the rest of the industry can learn from them. In September, the Overall Winner of the 2016 Facility of the Year Awards was announced: Genentech's Cell Culture Biologics Drug Substance Plant 2 (CCP2) in Vacaville, California.

For the last three years, the judging committee has been led by Jim Breen from Johnson & Johnson Supply Chain, an organization in the Johnson & Johnson Family of Companies – where he has worked at for almost 20 years. Breen also currently holds the role of Treasurer on the ISPE Board of Directors. Here, he delves into the history of FOYA and what the 2016 awards tell us about the latest industry trends.

Tell us about the history of FOYA…

ISPE established FOYA more than 10 years ago and the goal is very simple: to recognize and celebrate great manufacturing facilities and the teams behind them. A good facility is essential for producing high quality medicines, but creating an effective facility is no easy task, particularly given the time and cost pressures on today's industry. As well as recognizing stand-out facilities, FOYA promotes good facility design, methodology and technology to the wider pharmaceutical community, so that more companies and engineers can be inspired. At the moment, we don't typically give out awards to R&D laboratories – our focus is on manufacturing or clinical plants, which closely aligns with ISPE.

The first FOYAs were awarded in



2005 (with the overall winner being Novo Nordisk's manufacturing plant in Hillerød, Denmark), but specific categories were not introduced until 2007: Facility Integration; Project Execution; Equipment Innovation; and Process Innovation were the first categories. In later years, categories for Operational Excellence and Sustainability were introduced. The increase in the number of categories shows how the industry as a whole has changed over the last decade. For example, sustainability wasn't such a hot topic 10 years ago, but a large number of companies today take this very seriously.

How are the awards judged?

We have judges from both small and large companies. Over the years, we've expanded the eligibility and requirements for the awards, and now we tend to receive anywhere from 20 to 50 applications every year. The judges review these and we all meet to debate them. It's a very democratic process. Our judges have experience from all over the world and are very familiar with the latest trends. They know when companies try to stretch the truth – indeed, they are adept at spotting real innovation that can have an impact on the industry. Companies submit their entries for the categories that they want to win or feel are the best fit, but sometimes after reading the entries and doing our own research the judging panel may apply them in a different category. We also give out Honorable Mentions for companies that don't necessarily meet

Rising from the Ashes

By Stephanie Sutton

Genentech's Cell Culture Biologics Drug Substance Plant 2 (CCP2) in Vacaville was originally conceived in 2004, but it was closed in 2010 – before it could produce a single product. At the time, it was expected that biosimilars would strongly undercut the innovative biologics market. With a very strong biomanufacturing footprint, Roche (which acquired Genentech in 2009) took the decision to close the site to avoid having excess capacity. However, the site was not sold but kept in a returnable site with the infrastructure intact – in case it was ever needed.

Just three years later, Roche announced that the Vacaville facility would be reopened. Particularly in the US, biosimilars have had a slow start, and during the same time Genentech and Roche have seen rising demand for biologic oncology drugs – with their inventory reaching critically low levels. In September 2013, the decision was made to fast track the facility's restart. Although the facility had been state of the art when first built, change can happen faster than expected in the pharma business landscape – the new facility needed to be brought in line with the latest GMP requirements, regulations and sustainability directives. In particular, the site needed improvements in environmental microbial control, manufacturing control and automation. Genentech had to bring in a number of contracting firms and people from the company's other sites. In addition, the company also brought in patients to speak about their experience with cancer to remind workers about the end goal of the project.

The plant reopened in January 2015 and uses some of the largest scale cell culture production equipment in the industry (8 x 25,000-L bioreactors; 1.8 m diameter chromatography columns; 7 clean-in-place skids for both upstream and downstream areas) – able to provide oncology products to more than 500,000 patients annually. As well as being the overall winner for FOYA, the company won the Process Innovation category.

the FOYA criteria, but have nevertheless achieved something impressive.

In terms of judging criteria, we are always looking for innovation, particularly that of a disruptive nature. Safety, however, is the most important consideration; the goal of the industry must always be to provide patients with products of the highest quality. If a project does not have a good safety record then we typically eliminate them from consideration. We also focus on the team. Running an effective facility is a team effort so we look at how the team participates in the whole project to make it a success.

What do the 2016 winners tell us about current industry trends?

Generally speaking, in today's industry companies have to be flexible and adaptable because the industry is changing rapidly. In addition, it is crucial to be as cost effective as possible while still maintaining high quality standards. A lot of advances are being seen in the industry – not only in terms of new drugs and drug development technologies, but also in manufacturing methodologies; for example, there is a move to minimize the use of space-consuming cleanrooms, a move which reduces air conditioning, air changes and utility usages, and to use closed production instead.

At the same time, companies also need to be able to react to public situations, such as disease outbreaks or drug shortages. To this end, speed is becoming crucial. This year, the winner of the Equipment Innovation category was Pfizer, for its investment in modular manufacturing equipment (GEA's ConsiGma 25 system and G-CON's modular POD system). The technology is all about speed of deployment – and I found Pfizer's move particularly interesting because the company can now use its equipment to relatively easily set up manufacturing in any country, without having a large footprint.

The two Honorable Mentions for 2016 are also fascinating. Greater Pharma Manufacturing's new facility in Thailand was one winner and shows how companies in developing countries are seeking to catch up with western standards. Around 15 years ago, visitors from ISPE told companies in Thailand that they needed to bring their manufacturing up to a higher standard – and Greater Pharma Manufacturing's facility is a direct response to this. The company has applied western standards to the design, build and operation of the facility. It is the first plant in Thailand to use closed processes from raw material to finished product.

The second Honorable Mention went to the University of Strathclyde in the UK for the development of its Technology & Innovation Centre. The project did not meet the criteria for an award because the center is designed to support partnerships rather than be used for commercial or clinical manufacturing, but it is a good example of an effective public-private partnership. These types of partnerships will be important for the future of the industry. And of course, the students working in the center may well become pharmaceutical professionals in the future.

Another company I'd like to highlight is Ethicon, which is part of the Johnson &Johnson Family of Companies, where I work. Ethicon won the 2016 FOYA (I did not take part in the voting of course) in the Sustainability category for reducing the environmental footprint of its facility in San Lorenzo (Puerto Rico). The site was first set up in 1988 for the manufacture of medical devices, and the new sustainability efforts have reduced energy consumption by 26 percent and water consumption by 9 percent. At the same time, the facility's production volumes have increased by 11 percent compared with 2010. The reductions are in line with J&J's Healthy Future 2020 sustainability initiative – 20 percent of plants have to be using renewable energy by 2020 and then 80 percent of plants by 2050. It's not easy to make a plant more sustainable; water consumption can be particularly difficult to reduce. However, an increasing number of plants are paying attention to this important

area. There are some plants in India that are looking to have zero water discharge in the future.

How has the industry reacted to the awards?

Recognition is a powerful motivator – teams love to see that their hard work is paying off. It takes a long time to establish a new facility or to improve an old one and it is energizing to know that you are on the right track. For me personally, it is always rewarding to see the reactions of the winning companies. I think it's very important to recognize the achievements of the pharma industry and we widely publicize the award winners, which gives the teams a popularity boost. FOYA is not just about rewarding a company and its owners – a lot of the credit goes to the engineers and contractors. At the same time, publicizing the winners also allows other companies to learn from and be inspired by them.

As well as being able to give something back to the industry, I'm also very encouraged by the progress that the industry as a whole is making. I'm also constantly learning and then asking myself what I can do to make things better in my own role. I work globally, so it's great to see who is doing what – and whether the Johnson & Johnson Family of Companies are at the forefront or needing to up its game!

Do you have any predictions for next year's awards?

Over the last few years of FOYA, I've noticed that a greater number of small companies are submitting entries, as well as government-private partnerships. I'm also seeing contract manufacturing organizations winning awards. Overall, these trends show that the industry is not just about "Big Pharma" anymore so I expect to see more variety in the projects we receive in the future. I'd say that about half of the awards go to small projects. At FOYA, we always like to highlight the fact that the awards are not based on the science or size of the project, but on the overall standards and execution.

For 2017, we are adding a new category: Facility of the Future, which will recognize facilities that are reacting to potential future trends. I'm excited to see how this category works out next year.

Find more details about the awards at: www.facilityoftheyear.org

2016 Winners

Overall Winner & Process Innovation
Genentech; CCP2 Return to Service
Location: Vacaville, California, USA
Project: Fast track restart of a previously closed biologic facility

Equipment Innovation
Pfizer; The Portable Continuous Miniature and Modular Collaboration
Location: Groton, Connecticut, USA
Project: Formation of a consortium (Pfizer, GEA and GCon Manufacturing) to design and build a portable, autonomous manufacturing environment for continuous oral solid dosage production

Facility Integration
Takara Bio; Center for Gene and Cell Processing Construction Project
Location: Kusatsu, Shiga, Japan
Project: Construction of a facility that houses cell products, viral vectors and recombinant proteins

Operational Excellence
Baxter BioPharma Solutions; Baxter Biopharma Solutions (BPS) Oncology Manufacturing Expansion
Location: Halle, Germany
Project: Adding additional capacity for parenteral oncology and other complex liquid and lyophilized products

Project Execution
Janssen Vaccines; ZEBOV in 81J
Location: Bern, Switzerland
Project: Fast-track refurbishment of a facility for Ebola vaccine production

Sustainability
Ethicon; San Lorenzo Conservation Strategy
Location: San Lorenzo, Puerto Rico
Project: Roll out of a sustainability program resulting in a 26-percent energy reduction

Honorable Mentions
Greater Pharma Manufacturing; Greater Pharma New Facility
Location: Bangkok, Thailand
Project: Application of western standards to the design and operation of a manufacturing facility in Thailand

University of Strathclyde; Project Technology & Innovation Centre
Location: Glasgow, Scotland
Project: Creation of a nine-storey collaborative research and conference centre designed to bridge the gap between academia and industry

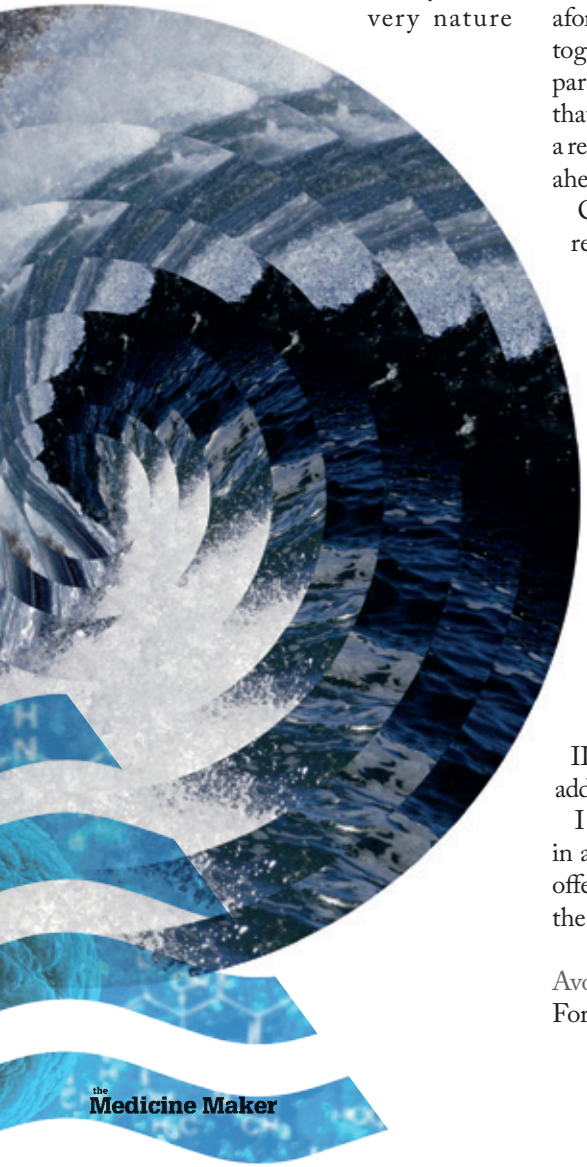
West Pharmaceutical Services; Kinston, NC Ready-to-Sterilize (RS) Expansion
Location: Kinston, North Carolina, USA
Project: Upgrade of a facility that produces components; implementation of lean techniques

Riding the Cell Therapy Wave

A surge of exciting new cell-based treatments is coming – but is the industry ready to manufacture them and catch the wave to success?

By Brian Hampson

It is clear that the manufacture of patient-specific cell therapies (PSCTs) involves unprecedented complexities. The most obvious challenge is that PSCTs, by their very nature (cells are extracted from a patient or a matched donor, processed and then returned to the patient), demand that an individual cell therapy product is made for each individual, eliminating all the efficiencies associated with traditional high-throughput drug manufacture. Furthermore, the process also differs from the manufacture of "normal" biologics on many levels, including regulatory, supply chain logistics, complexity of product attributes and the complexity of preserving and storing therapies composed of living cells. The good news? The cell therapy industry has evolved; developers, manufacturers, and regulators have all become better at addressing many of the aforementioned challenges. By working together and thinking laterally, these parties are devising innovative solutions that will make novel medical treatments a reality. But one key challenge still looms ahead: commercial-scale manufacturing.



Current PSCT production processes require an abundance of cleanroom space, operational expertise and expert personnel, and incur significant overhead costs. As a consequence, current cell therapy manufacture is generally not viable at a commercial scale.

Nevertheless, projections from Informa and the Alliance for Regenerative Medicine suggest that a tsunami of potential PSCT products is approaching: in 2014, there were 378 regenerative medicine trials (39 in Phase III and 206 in Phase II), and by late 2016, that number rose to 801 (68 in Phase III and 467 in Phase II) (1). Clearly, there are good reasons to address the scalability issue.

I covered the manufacturing problem in a previous article (2). Here, I'd like to offer practical advice that forms part of the solution.

Avoiding wipeout

For cell therapy manufacturing to be commercially successful, a systematic development paradigm should be used; Development by Design addresses quality, cost of goods (COGs), scalability, and sustainability – failure to balance any one of these elements may lead to a "wipeout". Automation – along with other approaches, such as integration, elimination, simplification, and sharing (see sidebar, Automation Strategy) – can help optimize many of these factors.

Quality

Quality is foundational for all therapeutics. However, the manual, open, and human-dependent nature of many PSCT process steps can make it difficult for manufacturers to meet the critical quality attributes (CQAs) of the final product. And it is often impractical to perform the complete range of lot-release tests required to confirm that all CQAs are met for each PSCT lot. How can we develop a robust process that can consistently produce high quality material? Well, automation (and related process optimization) can improve quality in at least two ways. First, automation significantly reduces the risk of human errors, such as mistakes in data recording/calculations or errors in the performance of manual process steps. Second, it reduces process variability. Despite excellent training and experience, human labor is by nature variable (individuals may perform a given task differently to others or may not perform a task consistently from one day to another). Reducing variability (through automation and optimization) results in more reproducible processes.

COGs

The high COGs of PSCT products (typically driven by labor and testing costs) demand a proportionately high commercial value proposition. As clinical development progresses and clarity around the actual value proposition builds, it is critical to optimize commercial viability by

Figure 1. Idealized future state of PSCT manufacture.

focusing on COGs reduction. COGs minimization depends on many factors, including choice of raw material supplier, the decision to manufacture in-house or to outsource manufacture and, of course, where and how to invest in automation. As one example, an early cell therapy product was launched using a manual manufacturing process, with the aim of introducing cost-saving automation later. However, lower than anticipated demand for the therapy led to excessive COGs after launch. The manual nature of the process led to a relatively high direct cost of the product, resulting in significant problems for the cell therapy developer. An appropriate investment in automation prior to commercialization might have potentially reduced both direct and overhead costs, and better positioned the therapy for long-term commercial success.

Automation reduces the cost of manual labor (by cutting both the number of hours and the level of expertise needed), the cost of equipment and associated consumables (if several unit operations can be handled by one piece of equipment), and overheads (by saving on manufacturing time and space requirements). Labor costs, in particular, can have a significant impact on cell therapy COGs. Though automating one unit operation may only save one hour of labor per product batch in traditional pharmaceuticals (where one batch provides treatments for thousands of patients or more), with PSCTs, because one batch represents one patient, the hour of labor is saved over and over again.

One area of COGs that is often overlooked is the cost of adverse quality events, such as deviations and out-of-specification incidents. Each adverse quality event demands management and investigation, and the associated labor costs can rapidly escalate. In the extreme, an adverse quality event could result in a failed process that must be aborted, requiring that the sunk costs be absorbed as part of the COGs for successfully completed products. This is in addition to the wider implications of delay or failure to deliver the product, including impact on the patient, impact on accrual objectives and costs for clinical-stage programs – as well as diminished market confidence for commercial-stage

Automation Strategy

Automation strategy needs to address a range of considerations, including:

- process automation (closed-loop process control)
- task automation (for example, selection process, wash and formulate process)
- test automation (for example, compendial method)
- factory automation – information (electronic batch records) and execution (manufacturing execution systems or MES).

Automation is one of several strategies for manufacturing optimization that also includes:

- sharing (performance of more than one unit operation by the same technology)
- integration (combining two or more unit operations into one)
- simplification
- elimination (identifying steps that are not necessary to meet the product's required attributes).

Risk Level	*Example*	*Timing to limit risk*
None	Change to automated sterility test	Before BLA
Low	Change in process unit operation and "cell journey" is the same	Prior to 50 percent accrual in pivotal trials
Medium	Change in process unit operation and "cell journey" is similar	Prior to initiation of pivotal trials
High	Change in process unit operation and "cell journey" is modified	Some Phase II clinical data

Table 1. Managing comparability risk.

Considering Comparability Risk

A good surfer understands that each time a new wave approaches, timing – derived from a balance of experience and instinct – is crucial. Act too soon or delay too long, and you will inevitably go under. Likewise, certain criteria in cell therapy manufacturing can guide our judgment about when to automate.

A developer must consider the potential comparability risk of making changes to automated processes early or late in clinical development, and anticipate the implications. As dictated by the FDA, cell therapy developers must demonstrate that any manufacturing change does not significantly affect safety, identity, purity, or potency. Depending on the nature of the change and the requirements of product characterization, this demonstration of comparability between pre- and post-change product may only require laboratory testing. At the other extreme, it may demand additional clinical studies. A change to the manufacturing process presents a comparability risk even when it occurs early in a clinical development program, but much less is at stake than when changes are made after substantial clinical data has been generated.

Some process changes are associated with relatively low comparability risks, while others have relatively high risks. For example, changing from a manual to an automated method in a core process step, such as changing from a manual static culture process to an automated perfusion bioreactor, would present a major comparability risk. By contrast, the risk associated with switching from manual record keeping methods to automated electronic record keeping is minimal. The risk is lower, generally, when the change does not alter the journey that the cells are on. Some examples of change-risk relationships are listed in Table 1.

programs. A well-executed plan for automation can substantially reduce the occurrence of adverse quality events and therefore eliminate the associated direct and indirect costs.

Scalability

Crucial for the success of the cell therapy industry as a whole is the ability to migrate from a clinical-scale process, with the capacity to make tens to hundreds of patient doses per year, to a commercial-scale process that can provide thousands to tens of thousands of patient doses per year. For PSCT products, this means that the number of batches must increase. Treating exponentially larger numbers of patients necessitates exponentially larger staff. The challenge of recruiting and maintaining trained staff limits the rate at which scale can increase – and where process complexity is high, there may not be enough qualified labor in the local geographic area to meet demand. Therefore, automation will likely be essential for scale-up. Furthermore, automation usually involves closed-system design, which can substantially shrink the physical footprint of the facility, and simplify infrastructure (for example, controlled non-classified space instead of ISO 7 cleanrooms). The result is shorter timeframes and lower investment burdens.

Sustainability

Automation can solve many manufacturing challenges – but not all of them. Even if quality, COGs, and scale objectives are met, there is the danger that manufacturing cannot be sustained over the full product life cycle. A key risk is disruption of the supply chain, which for cell therapy is still immature and relatively fragile. In the worst case, where a process step relies on supply chain elements that become unavailable, continued production will require manufacturing changes to be developed, tested, and demonstrated to be comparable. In many cases, automation

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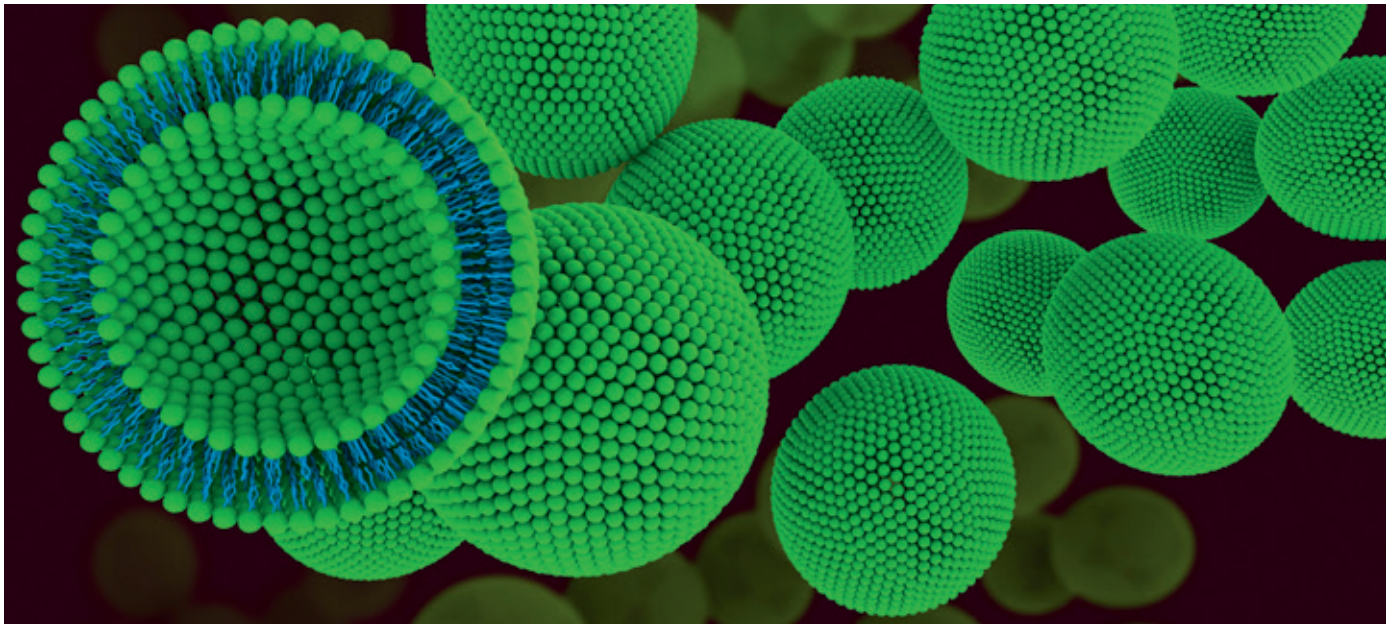

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technology is proprietary to its developer, and presents a sole-source supply chain. In these instances, it is important to assess the risk of interrupted access to the technology, such as equipment, consumables, technical support and service, and to establish suitable risk mitigation strategies.

Although automation can present supply chain challenges, it can also improve sustainability, if applied carefully and strategically. For example, automating materials handling and logistics can help manage relationships with suppliers, particularly as scale increases towards commercial requirements, by providing the developer and supplier with real-time data on demand and supply.

In terms of commercial sustainability, monitoring process consistency over time will be critical. Automated collection of process data helps to efficiently track and identify trends in data, which can be extremely beneficial in, for example, ensuring that product specifications are maintained over time. Additionally, this type of automation can reduce labor requirements significantly compared to manual extraction of data from hundreds or thousands of batch records.

Automation: surf's up?

I hope you will agree that we have established that automation is a key part of achieving commercially viable PSCT manufacture, but how do you choose solutions? A full knowledge of the landscape will ensure that you're able to choose automation technology that exploits the best available solutions for specific process requirements. Let's be honest: it's not in anyone's best interests to re-invent the wheel when a wheel works just fine! Unfortunately, there is still an unmet need for cell processing platforms that can perform a variety of cell manipulations across a range of scale – but innovation is starting to happen. For example, automated, programmable counter-flow centrifugation (CFC) platforms are being designed that can operate with single-use systems. Such platforms will help reduce the need for highly skilled staff and high-specification cleanrooms.

As mentioned earlier, despite the main advantages of automation, there are times when the justification – the return on investment – just isn't there. Consider a switch to automation that costs $10 million to develop, but only saves $100 per product. If a cell therapy developer plans on making only a small number of treatments over the life of the product (many PSCTs target rare diseases, for example), then the return on investment of $10 million certainly does not justify the investment. It is crucial to strategically consider whether the upfront cost of automation will be balanced by later savings in cost, time and labor.

It is also important to bear in mind that automation is only as good as the programming and direction given. If an automated process blindly moves things along in assembly-line fashion, but cannot gracefully detect and respond to errors or failures, the perceived benefits could quickly be outweighed. If an automated process produces flawless product most of the time, but fails in one out of every 100 runs, then one out of every 100 patients cannot be treated. Not only does this have serious implications for the patient, it leaves a PSCT product that cannot be reimbursed.

To help inform automation decisions and other manufacturing considerations, it is important to work with a manufacturing team – either internally or at a contract manufacturing organization partner – to strategically plan for commercial manufacturing needs. Plans should include:

- A thorough breakdown of the current state of a developer's product and process (for example, quality target product profile, CQAs, and unit operations).
- Analyses (for example, process capability analysis, quality risk analysis, COGs analysis, scalability analysis, sustainability analysis, technology and landscape analysis).
- A development and optimization strategy that provides a roadmap to a future commercial state.

Planning allows the cell therapy developer to apprise and align its stakeholders, make informed choices about further development, prepare for future unit operations and project COGs both at commercial launch and post-launch.

For the cell therapy industry as a whole, and PSCTs in particular, to truly become commercially viable, we must envision and develop a radically different future state of manufacturing, which is likely to have at least some of the attributes noted in Figure 1 on page 37.

Cell therapy manufacturing must largely move away from the cleanroom model and into the "back of the facility" – into production spaces more suited to high-volume production. That is not to say that cleanrooms have no place in cell therapy; however, whenever automation, integration, and closed processing systems result in a simpler manufacturing space that is used for multiple processes simultaneously, your bottom line will be healthier. And a healthier bottom line helps carve a world where cell-based therapies are accessible to all.

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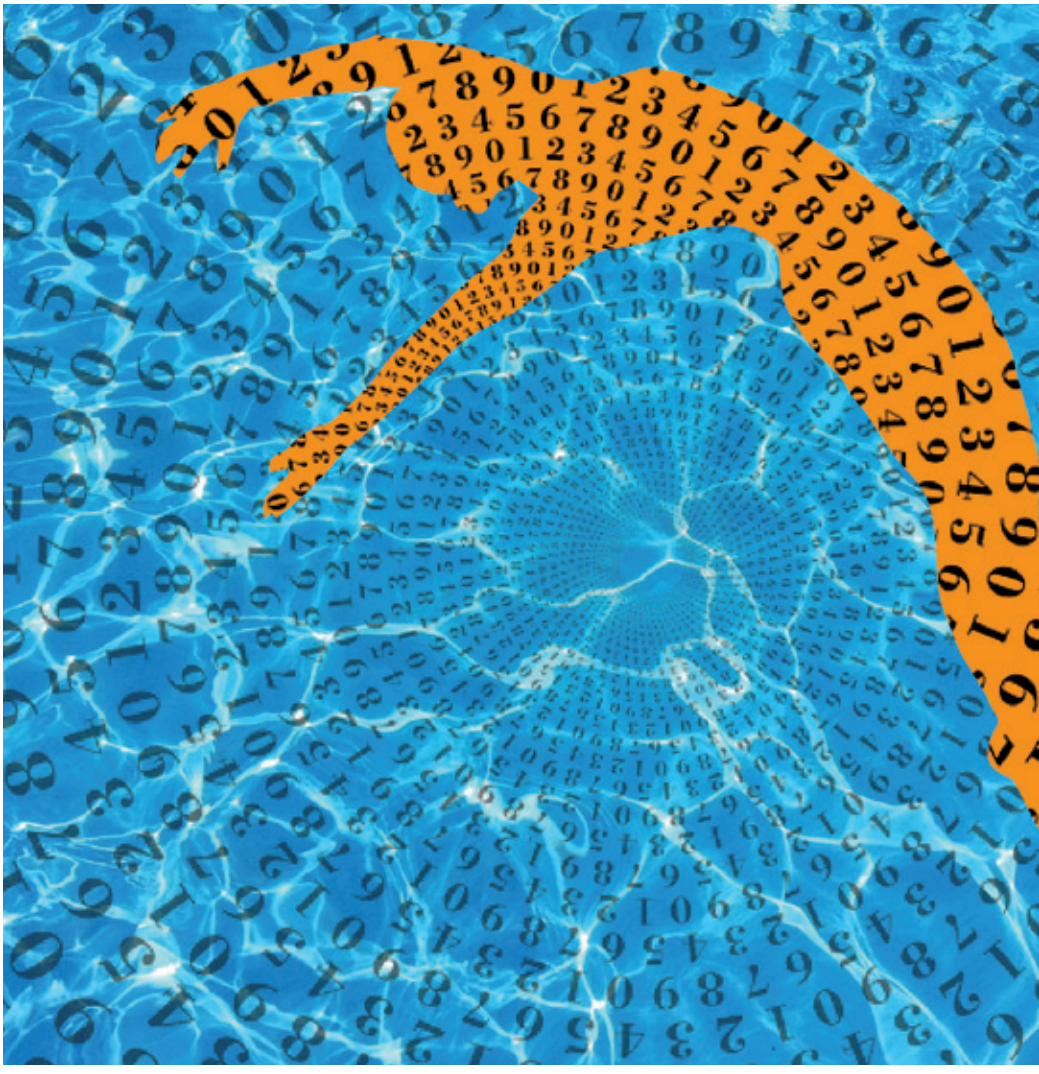
Time to Dive into Design of Experiments

Data, data everywhere... But pharma is not making the most out of it. Multivariate statistical modeling can play a key role in Quality by Design. Here's how.

By Jasmine



Over the last few years, medicine users have seen an upsurge in news about pharmaceutical quality complaints, including shortages of essential and life-saving drugs, safety and efficacy cases, and market recalls for extraneous matter. No doubt all of us involved in developing and manufacturing products in the industry have our own tales of woe: late approvals, out of specification (OOSs), out of trend (OOTs) results, repeat corrective and preventive action, issues with scale up or analytical method transfer, sampling errors, shelf life issues... The list of potential problems goes on.

Quality by Design (QbD) has been hailed as a panacea for all these troubles. I am an advocate of QbD and believe this claim is not too far from the truth. After all, most quality issues are inadvertently designed into products. With a good design strategy, it is possible to minimize the possibility of quality issues ever arising during a product's lifecycle.

In my last article for The Medicine Maker, I discussed the use of Design for Six Sigma (DFSS) tools for QbD-based product development (1). The article described Six Sigma as a data-driven approach to making more effective decisions for better quality products. The conversion of data into information is brought about by statistics – and DFSS involves a number of statistical tools too. Statistical tools help make data-driven decisions – decisions that do not rely on hierarchy, emotions or politics. The most common area for the use of statistics in pharma is limited to the clinical space where the number of patients enrolled, power of studies and hypothesis testing are everyday topics. Outside of the clinical and bioequivalence areas, the full potential of statistical methods has not been realized.

For this article – my third in this series for The Medicine Maker – it's time to discover how QbD and statistics can help to avoid quality problems.

Modeling data: a lucrative target

Why is it important to model data in pharmaceutical product development? Scientists in pharmaceutical laboratories perform experiments every day to validate scientific hypothesis – not just to generate data, but rather to create information and make predictions. In the current environment, industries are increasingly operating in tighter economic conditions, which means they are on the lookout for operational efficiencies anywhere and everywhere, including in R&D. At the same time, vast amounts of data are available and growing exponentially year on year. But without a structure or business

context to give data meaning, most information resources remain largely untapped because of lack of in-depth and relevant analysis. It is a huge waste of a very valuable resource, particularly in a competitive business environment, which is where data models come in (2). In fact, the pharma industry generates so much data that it is potentially a lucrative target for big data analytics, which could help make R&D faster and more efficient, and also help develop adaptable clinical trials and improve safety and risk management for patients and businesses (3).

But let's handle this one step at a time and start with small data first. Here is a very simple illustration of the motivation to model. Let's assume a few experimental runs yield data of values of response variable (Y) at certain conditions of an influencing factor (X):

X	Y
38	75
36	72
32	85
31	82

These four data points show what happens to Y at values of X. A model, on the other hand tells us, with a known level of confidence, what happens to Y at every data point in the range of Xs studied. You don't just know what happens to Y at X= 31, 32, 36 and 38 – you know everything that happens to Y in the entire range. A simple model for this data looks like:

$$Y = 131.3 - 1.542\,X.$$

Our little model is now like a genie. Let's say that Y is a particle size distribution (PSD) result and X is a crystallization parameter – the genie tells you based on your customer requirement of particle size how your crystallization process should be optimally performed to keep your customer happy. In pharmaceutical parlance, models help build relationships between critical process parameters (CPPs) and critical material attributes (CMAs), as well as what is critical to the patient – critical quality attributes (CQAs). These modeled relationships help establish design spaces and operating ranges for reliable product manufacturing. It is very important to note that in the absence of models, any decision on processing parameters and material attributes can be very short sighted, subjective and prone to biases introduced by different entities involved in the data generation and analysis. Judgement based on limited evidence also has a low probability of being successfully reproduced at scale. I've even seen occasions where something cannot be reproduced in the same lab again. Processes developed purely by the OFAT (one factor at a time) approach are examples of such risky processes.

"With a good design strategy, it is possible to minimize the possibility of quality issues ever arising."

The model maker

Scientists and engineers learn both pure and applied sciences primarily based on deterministic models. While these models help build our first association with building relationships between a set of factors and responses, they almost always rely on the premise that nature sits idle when processes happen. Remember the ideal gas equation PV=nRT? This is a deterministic model, but we all know that variation is nature's only irreducible evidence (4).

Stochastic models are statistical models that take into account randomness and can predict with a greater level of accuracy what may happen tomorrow. There are also "hybrid" models that build stochastic elements into deterministic models. Figure 1 illustrates the difference between deterministic versus stochastic modeling – stochastic models are best and most economically built from a set of designed experiments (DoE). The premise of QbD-based product development is to be able to predict real-world relationships between inputs and outputs – reproducibly. Statistical models help us with "real world" and "reproducibly."

DoE first began with the optimization of a potato crop field based on irrigation pattern, choice of seeding pattern and nutrient ratio. If the unfortunately common practice of OFAT had been employed by Ronald Fisher, who is considered the father of DoE, who knows how long it would have taken Great Britain to become great enough to feed all of its war-ravaged hungry citizens again... DoE was born out of minimum resources to get maximum information.

I wrote about DoE in my second article on design for Six Sigma (DFSS) based QbD development. DoE is a part of the "design" phase in the DMADV (define, measure, analyze, design, verify) cycle. Although invented in a potato field, it was popularized in pharma's allied industry – fine chemicals – with companies like ICI and DuPont taking the lead. ICI and Du Pont gave DoE greater structure,

including the three-step approach to explaining chemistry – screening, characterization and optimization.

When designing agricultural field trials, Fisher said, "No aphorism is more frequently repeated in connection with field trials, than that we must ask Nature few questions, or, ideally, one question, at a time. The writer is convinced that this view is wholly mistaken." Nature, Fisher suggested, will best respond to "a logical and carefully thought out questionnaire" (5). Such a questionnaire is a DoE, which allows the effect of several factors – and even interactions between them – to be determined with the same number of trials as are necessary to determine any one of the effects by itself, with the same degree of accuracy. There are many reasons to choose DoE:

- Interactions: DoE explores the "real world" relationships between factors and responses – not just one at a time, but in a true multivariate way because it also explores interactions between parameters to yield rare responses. Interactions happen all the time in the real world. I personally once saw an advanced API intermediate, which behaved absolutely normally when tested for hygroscopicity and photo degradation (one at a time), turn from white to almost bright orange when subject to humidity and light together.
- Less experiments: There can almost be no comparison between resources required to obtain the same amount of understanding between OFAT and DoE. DoEs are built on principles from geometry, not just statistics, and are the most efficient way of gaining maximum understanding of a multivariate environment. Often, scientists work on complex pharmaceutical products and multi-step processes where no scientific theory or principles are directly applicable or applicable alone. Experimental design techniques become extremely important in such situations to develop new products and processes in a cost-effective and confident manner.
- Competing CQAs: It's not just the hunt for interactions in minimal experiments that make DoE lucrative to explain the "real world". More often than not, pharmaceutical products are characterized by multiple CQAs, each with different relationships with CPPs and CMAs. These CQAs sometimes compete in different directions for the optimal setting. As an example, while a higher temperature in a reaction may increase the impurity profile and hence reduce the safety of an API, it may also be important to achieve the desired polymorph content for the right therapeutic benefit. Such situations are also easily designed around using desirability profiling in DoEs and generating "sweet spots".

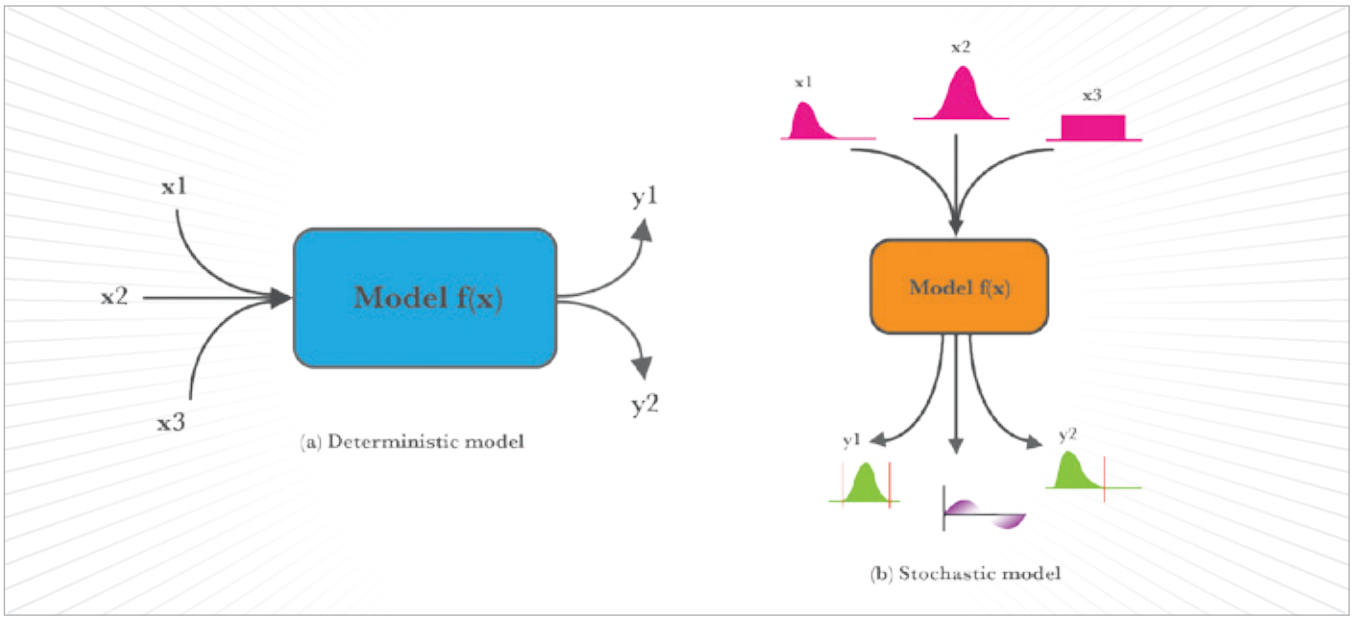


Figure 1. A simple illustration of a deterministic model (a) and a stochastic model (b) process – adapted from http://bit.ly/2hl2b1L.

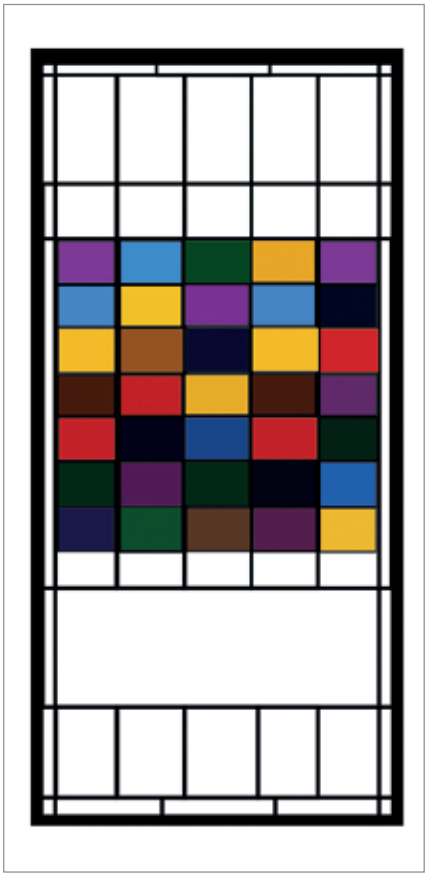


Figure 2. Displaying a 7×7 Latin square, this stained glass window in Caius College, Cambridge University, UK, honors Ronald Fisher – the inventor of Design of Experiments.

- Building robust processes: DoE finds relationships and makes predictions "reproducibly". Statistical models split the information from experiments into "signal" and "noise" – by doing this, they help us assess the true probability of an outcome versus a random event. Dig a little deeper and they will even be able to tell you which factor settings will give you a certain prediction interval (PI) of responses. PIs as opposed to point estimates can tell you what factor settings yield a certain response – not just once, but the probability of finding a response with an assumed confidence level and assumed number of times. Remember process capability indices like Cpk and Ppk? DoEs build these metrics into your process design.

How to DoE it!

DoEs begin in a cross-functional risk assessment evaluating the CQAs. Fishbone diagrams are commonly employed here to look at how Men, Machine, Measurement, Methods and Milieu affect the CQAs. Risk assessment tools, such as like Risk Priority Numbers, are used to select the critical few influencing factors for multivariate experimentation. Experimental ranges of these factors are then established from prior knowledge and experimentation. The objective of further experimentation (screening or optimization) is then decided, followed by selection of a DoE layout.

Screening DoEs are used to pick the "vital few factors from amongst the trivial many" as suggested by the Pareto Principle which was popularized by the QbD guru – Joseph M Juran. As an example, the titer obtained from a fermentation process can be influenced by molecular biology parameters, media recipe, and processing parameters, such as agitation, pH and temperature. Screening DoE, such as Plackett-Burman designs, fractional factorial designs and optimal designs, help identify which of these many factors have the strongest influence on titer. A screening DoE separates the many possible influences on a CQA into those that need to be studied the most to be able to best control the response. In the example of a fermentation process described above, the pH profile and media recipe maybe much more critical than the other factors studied earlier.

Characterization and Optimization DoEs, such as factorial designs, response surface modeling (RSM) and optimal designs, are then used to tune those key influencing factors to reach the target value of the response. These DoEs yield models with a high level of predictability over the experimental space. To optimize the fermentation process, a part of the pH profile and media recipe range studied in screening may be looked at more closely in optimization to establish a robust operating space.

"Progressive computing capabilities are making DoEs even more efficient and predictable."

Figure 3 shows the pharmaceutical QbD roadmap. Consider the step, "design space". This term, borrowed from the aerospace industry, means "design on earth what will happen in space". Given that our pharmaceutical products rarely go into space, design space for pharmaceutical product development scientists means design in R&D, keeping all possible things that happen in manufacturing, such as at different scales, and with different equipment, operators, raw material suppliers and analytical methods, in mind. Such process capability can be built into the product using DoE. Another form of DoE called evolutionary operations (EVOP) when used in manufacturing helps build the "continuous improvement" step in the

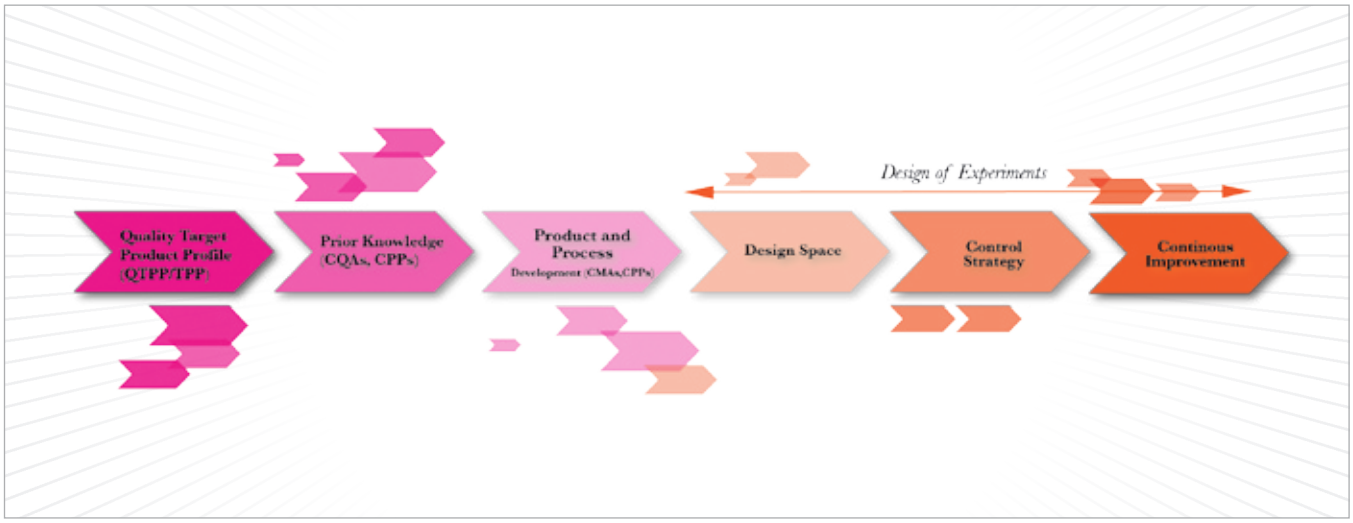


Figure 3. Pharmaceutical Quality by Design roadmap of experiments.

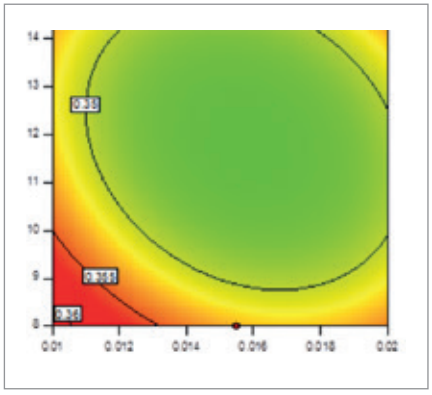


Figure 4. An illustration of a contour plot. A contour plot is easier to interpret than a 3D surface plot.

same pharmaceutical QbD roadmap.

Without DoE, we would probably never make design spaces. If you test factors one at a time, there's a very low probability that you're going to hit the right one before everybody gets sick of it and quits! (6). (As a side note, it would also be very difficult to make cool and colorful contour plots, such as the one in Figure 4, which are all the rage in regulatory circles these days.)

Sound science

A new advertisement by JMP, a statistical software for process development, says very relevantly, "Luck is Good, JMP is Better". Software, such as JMP, Minitab and Design Expert, have progressively made statistics easy to learn and use for the scientist. Statistics is also steadily finding its way into scientific curriculum. Progressive computing capabilities are making DoEs even more efficient and predictable. Sound science coupled with sound statistics in the form of DoEs has the unique ability to make better pharmaceutical products – which aren't plagued by OOSs, OOTs, analytical method variability, recalls and rejects that dampen the industry's morale and erode patient confidence in pharma products.

A while ago, I read an article in a Forbes magazine from 1996 about DoE (which the article referred to as "multivariate testing") (6). The article made a very compelling case to use DoE for increasing sales of movie theatres through free popcorn and to improve touch screens for ATM machines by changing the type of polyester and adhesive used. The article also said that OFAT became outdated more than seventy years ago, but it has taken an extraordinarily long time to trickle down...

Twenty years later, and it's still just trickling down into the pharmaceutical industry. To drive QbD to its logical end, let's turn this trickle into a downpour!

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Accessing Big Pharma's Conscience

Sitting Down With... Jayasree K. Iyer, Executive Director, Access to Medicine Foundation, Haarlem, the Netherlands.

Credit: Patricia Wolf

How did you get involved with the Access to Medicine Foundation?

I used to be a molecular biologist, developing malaria vaccines. The translation of research into improved global healthcare is very dear to my heart. Later, I became a negotiator between pharmaceutical companies and other public and private partners, focusing on funding solutions for neglected tropical diseases.

I joined the foundation because I was struck by their idea of using good quality data from companies to encourage them and others to do more to promote access to medicine. I believe that the vast majority of people in the medicine industry want to help others – at times, they need a little guidance on what they can do. I was Head of Research for two and a half years, before taking over as Executive Director of the foundation.

What is the goal of the Access to Medicine Index?

The index is an independent examination of what the Top 20 pharma companies are doing for the world's poor. It provides a series of staple expectations for the pharmaceutical industry and shows them how they can up their game. Even companies who are not included in the index use our criteria to help them formulate their access to medicines strategy and measure their progress. The index is also a place where practices can be shared between companies – as competitors, they don't always get that opportunity.

How are companies assessed?

We focus our attention on the 51 most burdensome diseases in 107 low-and middle-income countries. We ask: are companies developing drugs for these markets? And are they making them available and affordable to those who need them?

New to the index this year is an analysis of how well each company's priorities match up to priorities identified by external organizations – we want to know how responsive the industry is to international initiatives. For example, this year we looked beyond whether companies have affordable pricing schemes, to analyze whether the products and countries covered by the schemes match up to global priorities.

How did companies fare in this year's index?

It is a very competitive ranking, with companies jostling for position and often leapfrogging each other. GlaxoSmithKline (GSK) tops the index for the fifth time in a row, with Novartis, Johnson & Johnson, and Merck KGaA close behind. Novo Nordisk, Roche, and Gilead dropped this year, while new initiatives helped AstraZeneca and Takeda rise up the ranks.

Overall, companies are doing more. There were new initiatives, important new drugs reaching the market, and new approaches to doing business in developing countries. However, it is an uneven picture, with no progress in affordable pricing, and misconduct still a major issue.

Were there any surprises?

One thing that really stands out is how diverse the industry is – there are very few areas where the companies move as a pack. This diversity illustrates the different ways that access can be approached, and helps us to assess what works and what doesn't.

What are the common factors amongst high-scoring companies?

A key element is leadership. A company that truly believes in improving access and makes it a core part of their commercial strategy is going to do better in the index than a company that limits efforts to a few corporate projects. Companies that do well tend to be those that discuss access to medicines at the very highest levels. Any change in leadership can have a big impact, so it will be interesting to see whether GSK maintain their position at the top of the index after the departure of CEO Andrew Witty next year.

What areas need improvement?

One obvious area is affordability. True needs-based pricing is still rare, with only five percent of drugs meeting our toughest criteria for affordability.

Instances of corruption, bribery, anti-competitive behavior, and unethical marketing practices are still occurring. Companies need to take this very seriously – it's no good bringing access plans to the table if you aren't operating ethically in these countries.

Is improving access to medicines all down to pharma?

Absolutely not. There is a wider ecosystem of governments, regulators, investors, patient organizations, and NGOs – whose support we need to reach our goals. Treating the pharma industry as the "bad guy" is not the solution – working with the industry to come up with the right solutions and address the challenges is a much better bet. It's easy to say we want an endless supply of cheap medicines, but we have to look at how that can be made sustainable. For example, regulatory incentives and disincentives are crucial, and a lot of investors are now starting to look at access to medicine as part of their decision-making, which plays a huge role in motivating companies. In addition, governments need to carefully consider their policy on issues like generic drugs.

Tell us about the foundation's latest project – the Access to Vaccines Index…

It is the first ever tool that measures efforts to make vaccines accessible and affordable. The first index will be released in 2017 and is intended to act as a baseline measure of current performance, but also a guide to how the vaccine landscape needs to evolve if we are to solve some of the unique issues around vaccines, such as high production costs.

You can download the 2016 report at accesstomedicineindex.org.

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