JUNE 2019 # 54

the Medicine Maker™

Casting a Formulation Spell

Discover the magic behind the orally disintegrating tablet that won The Medicine Maker 2018 Innovation Awards.

Online this Month

The cannabis business is booming and pharma is looking to get in on the action with new business models and potential new drugs derived from the cannabis plant. We reported on pharma's fascination with the cannabis field in our May issue (available online at https://themedicinemaker.com/issues/0519).

But if you're keen to learn more about the science of cannabis, you may also be interested in our sister publication, The Cannabis Scientist, which has a brand new website at https://thecannabisscientist.com/

You can also keep up with the latest developments on Twitter @thecannabismag

And Instagram at www.instagram/thecannabismag

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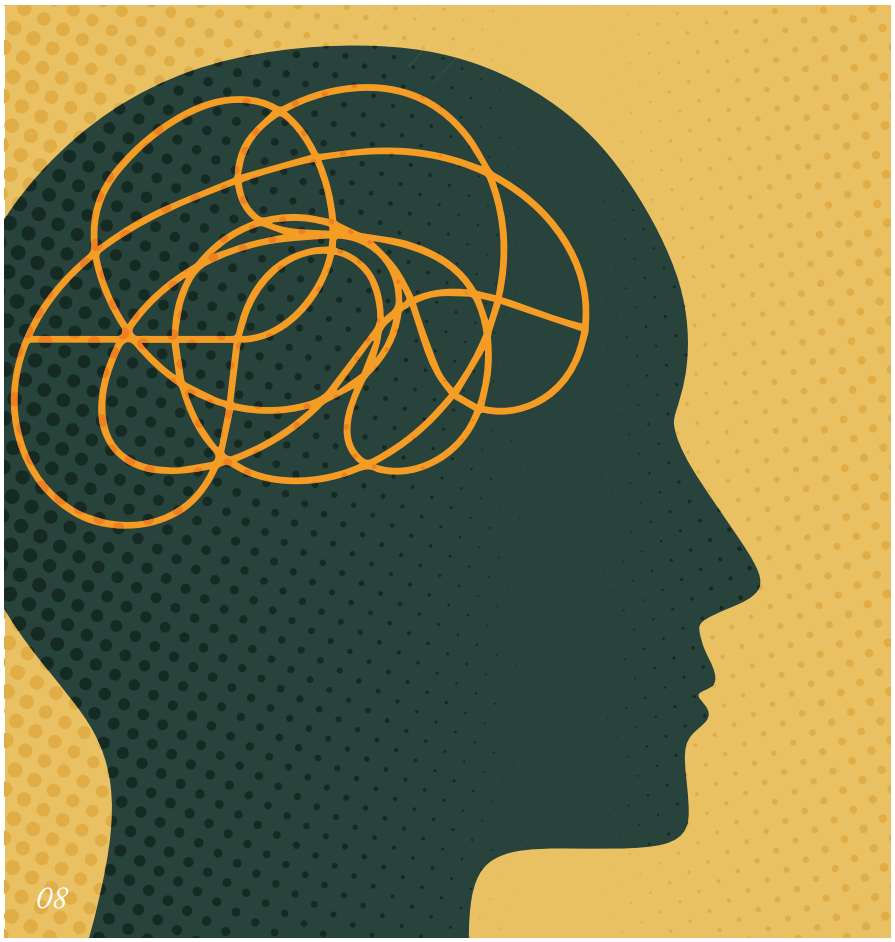
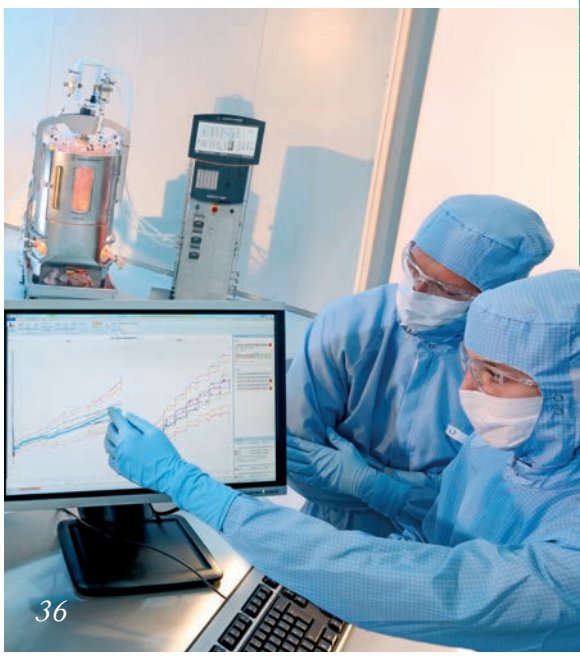
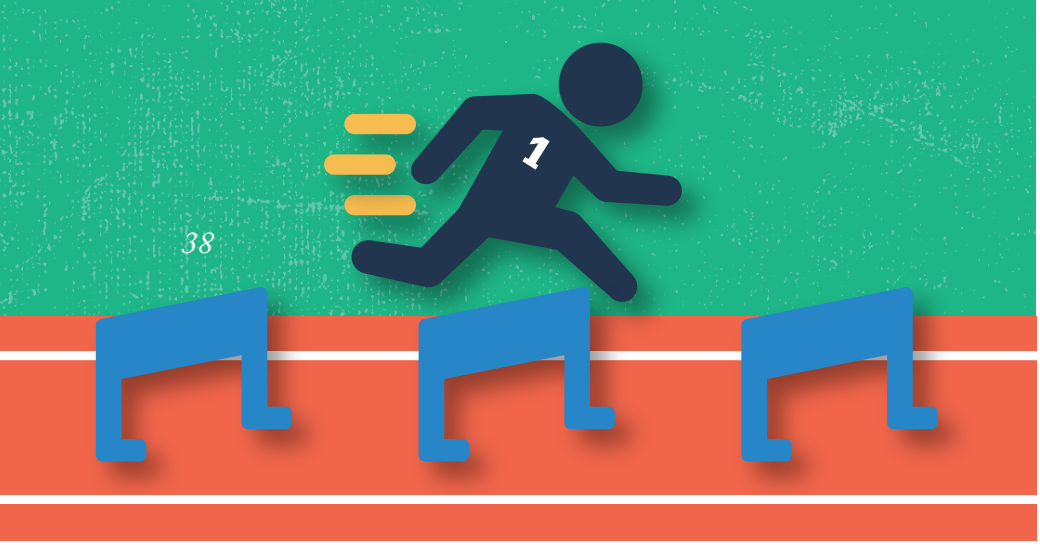




On The Cover

Celebrating the grand winner of The Medicine Maker 2018 Innovation Awards: Zydis Ultra developed by Catalent Pharma Solutions.



NextGen

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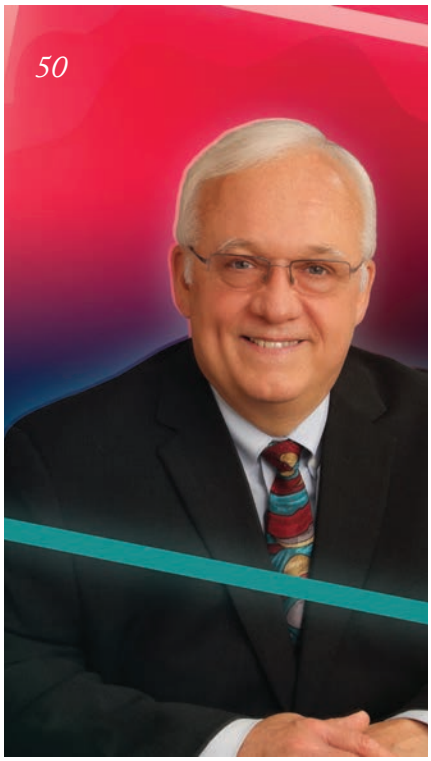
Reports



Sitting Down With

the Medicine Maker

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Looking on the Bright Side

More gene therapies are becoming a reality, and that's great news for patients – despite the increasingly eye-watering price-tags.

Pharma is in the news again – for both the right and the wrong reasons. Novartis' gene therapy, Zolgensma, has been approved by the FDA to treat children under two with spinal muscular atrophy (SMA). If untreated, children with type 1 SMA (the most common type) are unable to raise their heads, sit upright, cough, swallow or breathe easily. Only 25 percent of babies with type 1 SMA reach 14 months without needing daily machine ventilation – and many do not survive at all (1).

Of the 15 patients in the Phase 1 study, started in 2014, none needed permanent ventilation and all were still alive at the time of writing. And because Zolgensma is a one-time therapy, patients wouldn't have to undergo multiple spinal infusions each year, as with Biogen's Spinraza – the only other approved treatment.

The clinical results were impressive and it's great news that the therapy will be available to patients in the US. But much of the media focus has been on the price – a whopping $2 million, making it the most expensive therapy of all time. Is this a sign that voluntary pricing in the US has spiraled out of control? Or a fair deal for a life-changing and highly innovative therapy?

The price does (just about) fall within the upper bound of the non-profit Institute for Clinical and Economic Review's value-based price benchmark (2). And it's hard to disagree with Nathan Yates, economics and finance professor – and someone with SMA – when he argues in Stat News that the cost of Zolgensma is insignificant: "Think about the parents who will no longer have to receive the heartbreaking news that my parents were given 29 years ago: 'Your child has spinal muscular atrophy, and there's nothing we can do. Survival beyond early childhood is unlikely,'" (3).

Yes, price gouging in the pharma industry is a systemic problem. And nobody likes to hear, as we did last month, that companies have (allegedly) colluded to raise the cost of a drug by 700 percent (4). When it comes to life-changing gene therapies like Zolgensma, the concerns over the price are certainly legitimate, but I can't help but see the positive side; it's fantastic news for patients (and parents) that such treatment options are becoming a reality. And it's remarkable that we're able to have these debates at all.

James Strachan
Deputy 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

It's in the Blood

Using blood cells to test new drugs for neuropsychiatric disorders

Mental health disorders are the leading cause of disability worldwide and despite the starkly apparent need for novel treatments, a lack of understanding of the diversity of these disorders, as well as the processes underpinning them, have contributed to the steady decline of neuropsychiatric drug development programmes (by 70 percent) over the last decade. Another challenge faced by drug developers is the dearth of relevant pre-clinical models to test new hypotheses. To fully appreciate the complexities of neuropsychiatric disorders, there is no substitute for the human brain, but taking live brain samples from patients is a significant stumbling block for researchers!

But what if blood cells could be used instead? Researchers at the University of Cambridge, UK, have shown that peripheral blood cells taken from patients with schizophrenia can be used to identify drug targets (1).

"Despite their functional differences from neuronal cells, peripheral blood cells have multiple signalling pathways that are conserved across the cell types. By exploiting the signalling pathways, which are potentially relevant to the pathogenesis of mental health conditions, we have identified an ideal environment in which to test drugs," explains Santiago Lago, a postdoctoral research associate at the University of Cambridge.

The team used high-content functional screening to reveal novel functional drug targets, which are not observable by conventional quantification of genes and proteins in their resting state.These included repurposed compounds such as subtypes of L-type calcium channel blockers and corticosteroids for the treatment of schizophrenia. These functional drug targets can also be used to predict clinical responses to existing treatments.

"With documented safety, pharmacokinetic and administration data in humans, repurposed drugs can reduce the time and cost it takes to bring a new drug to the clinic. This is especially pertinent for neuropsychiatric disorders as it reduces the costly risk of failure, which has dissuaded many pharmaceutical companies from pursuing CNS candidates," says Lago.

The Cambridge researchers are now looking for clinical partners to test their drug candidates in proof of concept clinical trials, and will also begin to apply their high-content functional screening to other neurological disorders using larger patient groups. Finally, the group aims to explore the potential of their assay for treatment response prediction and personalized medicine applications.

While the group's study represents a positive step forward for the field, they are aware that the use of blood cells as a surrogate model to discover new drug targets and candidates for neuropsychiatric disorders may be met with some skepticism… "While this field of research has not has not been fully explored and warrants further investigation, an essential challenge still remains – to understand the biological basis of neuropsychiatric disorders and design personalized therapeutic strategies for them," says Lago. "We hope that our research will spark meaningful change to help address the critically unmet needs of patients with mental health disorders."

Reference

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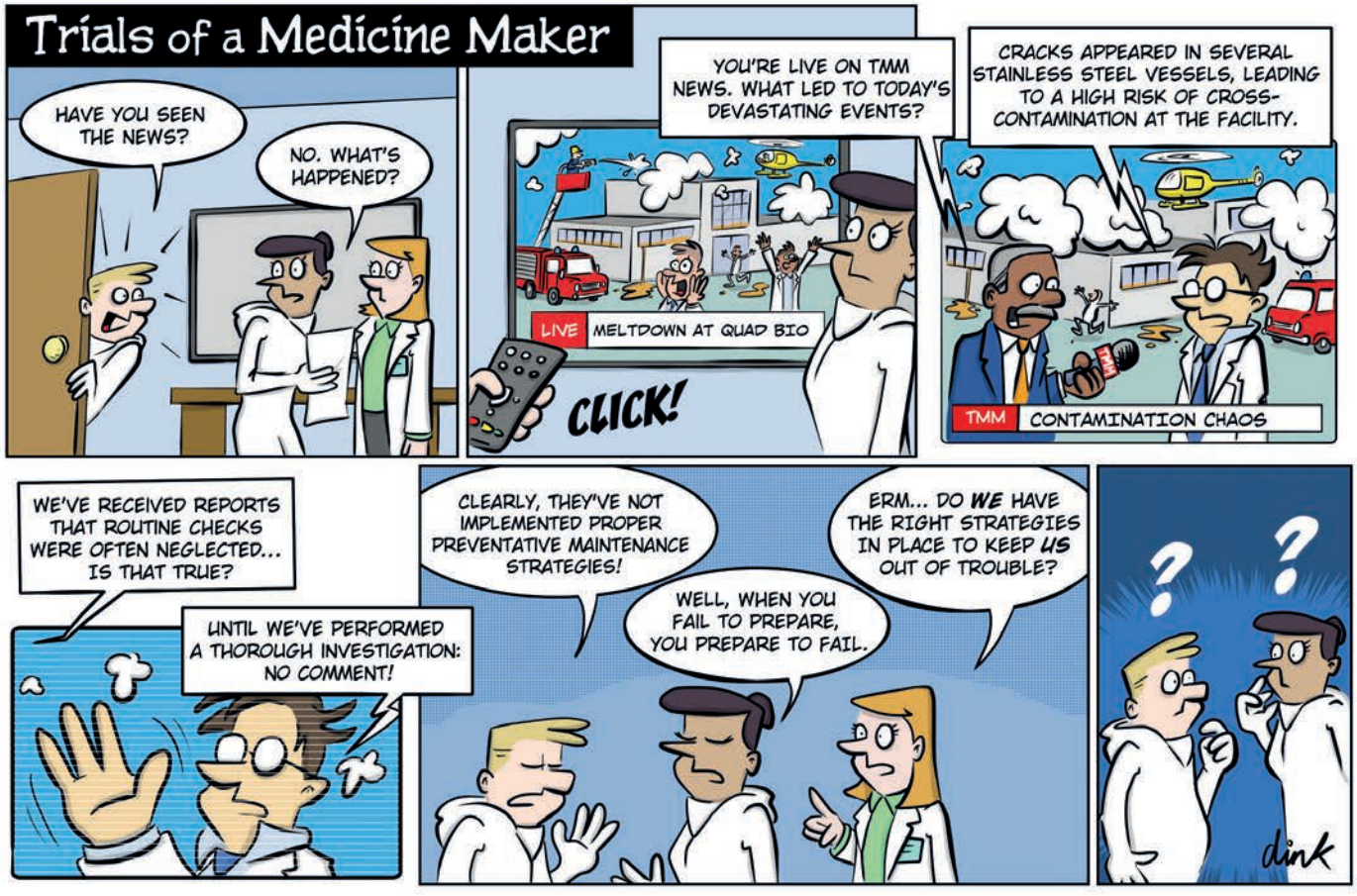
For more adventures featuring Gene and Eva check out our website themedicinemaker.com/additional-data/cartoons
If you have any ideas you'd like to see in future comic strips about bioprocessing then get in touch with us at info@themedicinemaker.com or look up #TrialsOfAMedicineMaker on Twitter.



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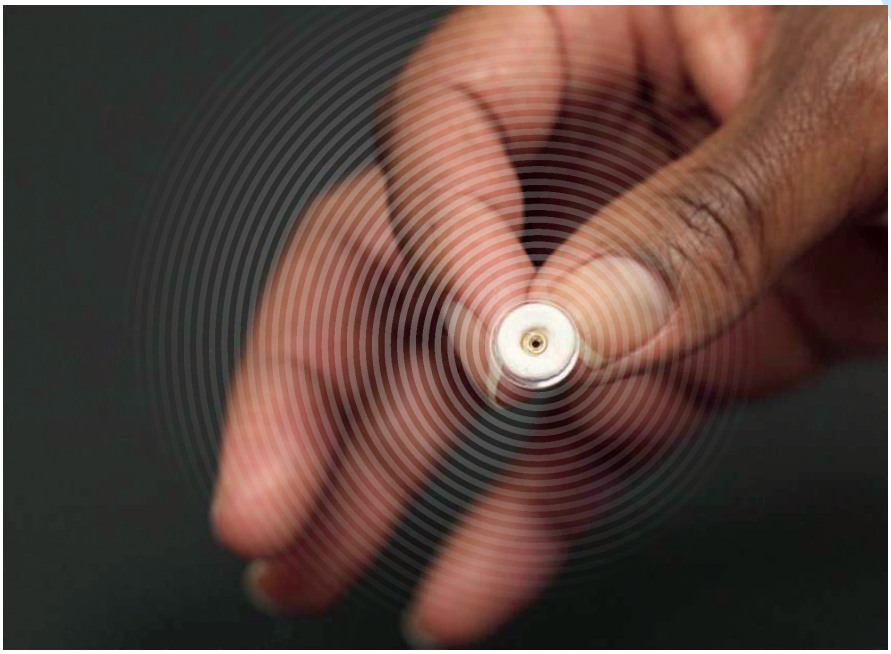
Designer Delivery

Transdermal patches coupled with jewelry offer a discreet method of drug delivery



We've all heard of transdermal patches for drug delivery, but what about drug delivery through jewelry? Researchers from the Georgia Institute of Technology have been experimenting with delivering drugs through earrings (1). For now, they have focused on the delivery of contraceptives, but the approach could be adapted to other therapeutics too.

"We have been working on a few different approaches to developing contraceptive delivery systems to make adherence to dosing schedules easier. Many contraceptives, such as daily pills, work extremely well if used correctly, but in typical use have lower efficacy because people forget to take the medicine according to schedule. In addition to facilitating improved adherence, we also seek to make contraceptive use discreet," explains Mark Prausnitz, Regents Professor and J. Erskine Love Jr. chair in the School of Chemical and Biomolecular Engineering at the Georgia Institute of Technology.

The skin is a formidable barrier and prevents the delivery of most drugs. However, there are a number of successfully commercialized transdermal patches that use drugs which are low molecular weight, lipophilic and low dose. Transdermal patches offer simplicity to the patient because they can be applied to the skin just once per week and left in place to continuously deliver contraceptive hormone. However, they aren't very discrete and transdermal contraceptives can come with side effects associated with estrogen administration (Ortho Evra has a black box warning in the US).

Prausnitz's team came up with the idea of "hiding" a transdermal patch in jewelry, such as earrings. "Many women are into the habit of putting on earrings and other jewelry on a daily basis, so associating the patch with jewelry could increase adherence. And by making a progestin-only patch using levonorestrel, we avoid the complications of administering estrogen," he says. "The biggest challenge was making the patch small enough to fit onto an earring back or to be incorporated discreetly into jewelry. We accomplished this by using an electrospinning method to fabricate the patch."

There was also the challenge of ensuring the controlled release from the patch was enough to be effective. Contraceptive tablets deliver daily boluses of drug, which result in peaks and valleys in contraceptive levels in the body whereas a transdermal patch maintains a relatively steady contraceptive level in the body, which can have advantages. According to Prausnitz, a steady rate of drug delivery from the team's patch is achieved by maintaining a relatively constant contraceptive hormone concentration in the patch throughout the delivery process by keeping the solution in contact with the skin saturated with drug from the electrospun fibers that make up the patch matrix.

The patches could potentially be incorporated into other forms of jewelry too, but the researchers chose an earring back because the earring back offers a flat surface that is normally in contact with skin. "It is straightforward to adhere a small patch to the earring back and thereby sandwich the patch between the earring back and the skin," says Prausntiz. "Although the permeability of the skin on the earlobe is not the same as other parts of the body, it can still allow for adequate delivery of contraceptive hormone if the patch is designed for that skin site."

The team is currently working to further optimize the patch design and looking to perform additional preclinical studies of pharmacokinetics and safety in animals.

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The Smart Pill Bottle

Can a text message ensure the integrity of drug products?

Smart packaging options can protect against anticounterfeiting, prolong shelf life and help improve patient compliance. However, the costs associated with the manufacture of smart and digital packaging, particularly sensors, often means that it is not available where it is needed most. With the aim of improving the availability of sensor technologies at lower costs, researchers at the King Abdullah University of Science and Technology, Saudi Arabia (KAUST) have developed a smart pill bottle that sends wireless alerts to patients' phones when it detects signs of tampering, unsafe storage conditions, or overdose.

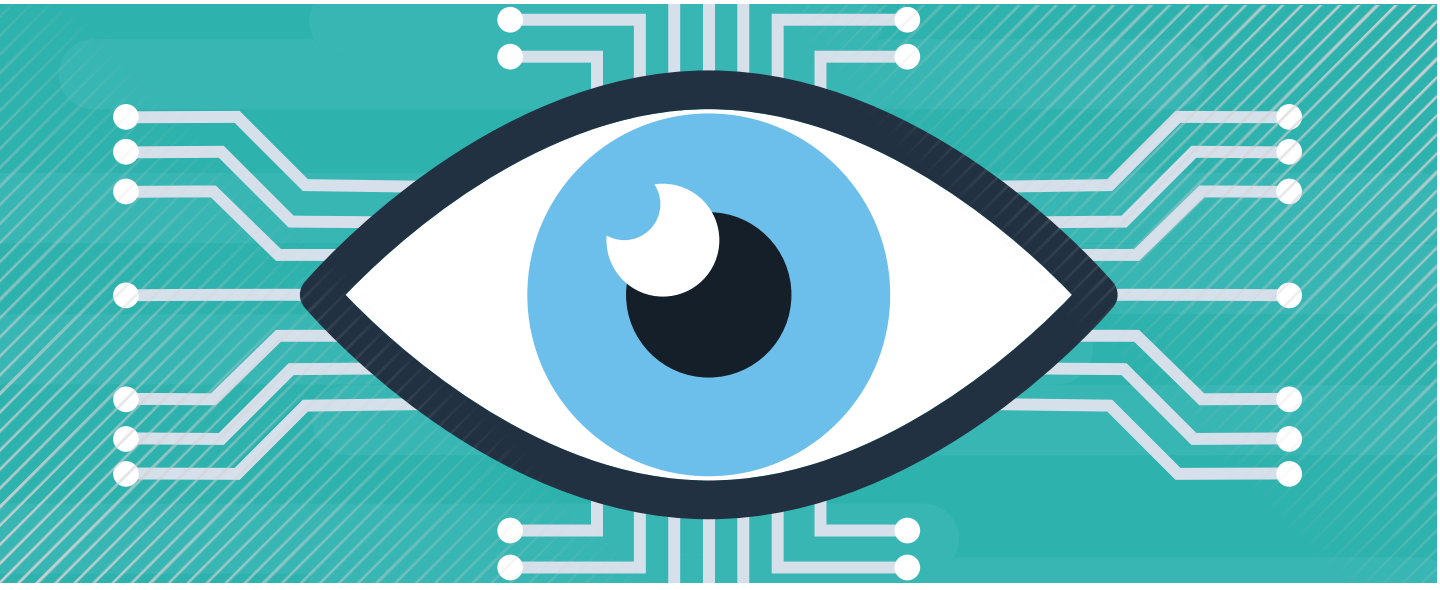
"While sensors hold a great deal of potential, currently available options can often be too bulky for real-life applications," explains Muhammad Mustafa Hussain, Professor of Electrical Engineering at KAUST. "Smart labelling technologies are often limited in their functionality and lack effective communication networks and data integration techniques to help companies adequately support patients."

Hussain and his team developed a sensor with touch-sensitive application. It is unconductive in its normal state but when pressed by a finger, the electrical connections enable signals to be sent to an external reader. Using 3D printing, the KAUST team created a pill bottle lid that relies on light-emitting diodes to count the number of pills dispensed and added temperature and humidity sensors made from paper (with circuits drawn in conductive ink) to the underside of the lid.

"Tamper-proof packaging ensures the integrity of products with sensitive and complex ingredients. It is vital that we are able to ensure the quality of drug products for patients. Our technology, when applied to pill bottles, can report signs of tampering and sub-par storage to end-users via mobile alert and support caregivers of patients with the propensity to cause harm to themselves through drug abuse," Hussain adds.

The research group intends to make their research open source so that others within the scientific community can replicate their design, particularly in deprived areas.

"We want to help empower people," says Hussain. "By giving researchers the opportunity to use our technology, we hope that they will open up broader horizons for the use of electronics for pharma."



Benevolent Action

Could harnessing the power of artificial intelligence put an end to the leading cause of sight loss in the developed world?

Artificial intelligence is fast-becoming crucial for the future of pharma. The ability of these platforms to comb through large, often complex databases through the application of big data analytics is one that many companies are keen to take advantage of. BeneloventAI is one of many AI companies drawing the attention of the industry. Its AI platform makes sense of biomedical data through its computational and experimental technologies, and the company has become well-recognized for its partnerships with key industry players.

In one of its newest collaborations, BenovolentAI has teamed up with Action Against AMD – a research collaboration formed by four UK sight charities (Blind Veterans UK, Fight for Sight, the Macular Society and Scottish War Blinded). AMD or age-related macular degeneration is the leading cause of sight loss in the developed world and exists in two forms; wet and dry. While wet AMD can be treated if diagnosed early, no such treatments exist for the dry form of the condition, leaving patients with a distorted sense of vision and a loss of contrast sensitivity.

After using AI to review millions of scientific papers, clinical trials information, and additional datasets relating to AMD, the partners have identified seven existing drugs (either already in development or being used to treat other conditions) that have the potential to be repurposed to address early forms of macular degeneration.

"We have prioritized strategies and pathways which are different from the established lines of enquiry – thus avoiding anti-VEGF (a growth factor therapy) and other anti-angiogenic strategies, as well as the complement system," explains Dr Wen Hwa Lee, Chief Executive for Action Against AMD. "Since our efforts focus on early AMD, we looked for drugs which were well-tolerated, employed convenient delivery routes and, most importantly, affordable."

While the partners can't comment on the specific drugs identified, they are eager to share their progress with the community on the completion of their experimental validation work. Moving forward, Action Against AMD will be exploring future opportunities to work with BeneloventAI but is also open to partnerships with other groups. The charity group says, "To be effective for patients globally, Action Against AMD will focus on bridging scientific and strategic gaps in research ecosystems – both at a local and international levels. We want to bring together different research communities to work towards the challenge of stopping the progression of AMD for good."

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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

Overcoming Complexity

Complex formulations bring complex technical challenges – but also the opportunity to make better medicines that promote compliance.

By Robert Lee, President at Particle Sciences.

There are two key drug development trends that are reshaping the industry's approach to formulation, leading to a rise in non-traditional dosage forms, such as nasal sprays, drug-eluting implants and more complex products. Firstly, there is the issue of poor solubility, which often forces companies to use a more complicated formulation strategy. Molecular targets can be quite hydrophobic and the therapeutic molecules intended to interact with these targets are increasingly insoluble. Around 40 percent of marketed drugs, and as many as 90 percent of drugs in the development pipeline, contain poorly water-soluble APIs that will not be effective if formulated as a standard solid oral dose. For many developers, this may be viewed as a concern or a road block; however, it is also an opportunity. There are multiple techniques available to increase the solubility or dissolution rate of drugs and improve their delivery, such as amorphous solid dispersions, lipidic-based systems, and nanoparticle suspension formulations. And there are also new benefits in terms of protecting intellectual property as a complex product often offers numerous opportunities in this area.

Secondly, the industry is also witnessing an increase in applications made under the 505(b)(2) FDA pathway, which involves repurposing existing, marketed APIs for a different route of administration. Companies use this pathway to develop differentiated forms for approved APIs – often to improve patient preference and compliance. The generic drug market is highly saturated so developing improved products is one way of carving out a more profitable niche. 505(b)(2) approvals grew by 50 percent last year and with the rising cost of taking new chemical entities to market, I expect use of this regulatory pathway to continue to grow. The ability to leverage pre-existing safety and efficacy data results in reduced time to market, although repurposing an API into a highly optimized dosage form is a highly technical challenge.

With more and more companies adopting complex formulation strategies, either for repurposing or to solve solubility or bioavailability challenges, a number of advanced techniques are emerging. One example is nanomilling, which is increasingly being used to improve bioavailability of oral dosage forms. During the milling process, drug particles are reduced in size to below 1000 nm, and typically as low as 100-200 nm. The conversion to nanocrystals increases the surface area-to-volume ratio of the API, allowing for greater interaction with water which increases the API dissolution rate – the rate of dissolution is inversely proportional to the particle diameter.

When looking for new formulation avenues, it is important to remember that one size does not fit all. You need to keep your eye out for new technologies but also be able to critically evaluate them to see if they will work for your drug product. I believe it is prudent to have an arsenal of several drug

development technologies available so that you can evaluate all of them with your API to see which results in the target product profile. For example, if one of my company's clients was interested in improving bioavailability and decreasing food effects for an orally administered drug, we would evaluate nanomilling, lipidic systems, and solid solutions via hot melt extrusion or spray drying (depending on the physicochemical properties of the API, of course).

In many cases, companies choose to work with a CDMO because they don't have their own internal resources to carry complex product development projects forward and may not wish to invest in new infrastructure and technologies. In this case, however, it is important to remember that it's not all about techniques and equipment. While several CDMOs offer nanomilling machinery, for example, not all have the requisite knowledge on stabilizing nanoparticulate suspensions and the analytical capabilities. Similarly, drug complexity can be further compounded when you're working with DEA-controlled substances that fall under Schedule I–V, or highly potent compounds in general. These attributes add extra layers of complexity – both scientific and regulatory.

In my view, it is becoming increasingly difficult to formulate new chemical and molecular entities; many of the "easy" molecules have already been formulated and targets are commonly hydrophobic. It is clear to me that complexity is here to stay. We must also consider patients and regulators' desires for medicines that promote compliance. The factors impacting compliance – safer formulations with less side effects, lower doses with the same therapeutic benefit, more palatable formulations, less invasive delivery devices, etc – contribute to the need for complex formulations. Personally, I find this space really satisfying and diverse to work in. You have to understand the molecules you are working with and use technology and expertise to find drug delivery systems that match their physical properties and create a dosage form that delivers the target product profile. Complex products may mean that an "off-the-shelf" solution isn't the answer and people will be forced to think outside of the box. In turn, this will lead to more innovation through the development of proprietary technologies and inventions in the face of specific molecule or application issues. Ultimately, this can only be a good thing for the industry and for patients, who will benefit from more efficient and convenient medicines.

Going Native with Microfluidics

Technology that enables protein analysis in solution has the potential to unlock a deeper understanding of interactions – and how those interactions can be manipulated.

By Andrew Lynn, CEO, Fluidic Analytics, Cambridge, UK.

If you think about how (bio)therapeutics work, you will immediately note that interactions – either between proteins or proteins and other molecules – are key. Those interactions are enabled by the protein's conformation, which not only imbues each protein's unique functionality but can also change depending on the conditions in which it exists. We now acknowledge that proteins do not function alone and, therefore, should not be considered as isolated entities, but as part of complex networks that ultimately drive biological systems.

Now, let's think about how we analyze proteins. Does the protein typically exist in its native state when we study it? Are we getting a "true picture?" Techniques that rely on denaturation or digestion – or where the molecules must interact with a surface or matrix (or are fixed to a surface) – affect protein conformation (or the ensemble of conformations), which means that we are actually testing a proxy of the native solution-state protein. Indeed, the dominant techniques for measuring protein-protein interactions, such as surface plasmon resonance (SPR) or bio-layer interferometry (BLI), rely upon fixing a protein to a surface to detect binding to an interaction partner, and thus may not be an accurate representation of the interaction in the biological system.

This is the challenge we want to address at Fluidic Analytics. We want to study protein interactions with as little interference as possible. In the pursuit of this challenge we investigated the use of microfluidic technology. But first, a little background.

The fundamental principle of microfluidic diffusional sizing (MDS) came out of Tuomas Knowles' lab at the University of Cambridge. The team realized the potential of the technique in allowing native state analysis of proteins and protein complexes with high accuracy down to low concentrations. The original findings were published by Yates and colleagues back in 2015 (1).

Even in 2019, there are relatively few off-the-shelf microfluidic instruments, so most research takes place on home-built rigs with custom chips, making it the domain of experts with specialist equipment. And athough reduced sample consumption is beneficial, the small volumes and path-lengths used in microfluidic devices can create challenges around detection sensitivity. Reproducibility can be another key issue, which is why there's a movement towards standardized instruments. By standardizing the technology, researchers can harness all the benefits of microfluidics, without the headaches and time-consuming process of chasing reproducibility.

Fluidic Analytics was spun out to develop Knowles' original concept into microfluidic instruments that would allow anybody to achieve accurate and reproducible results with MDS in a "plug and play" format.

There are a number of benefits to a microfluidic system. We've already mentioned the first two obvious advantages: reduced sample consumption and greater reproducibility – both crucial to reliably gaining insights from precious samples at the early stages of development. However, there are further benefits to MDS that are more fundamental.

At the microfluidic scale, fluids behave differently than they do in bulk. MDS actively harnesses this fundamentally different behavior to eliminate turbulence. This allows proteins to be characterized in solution, without artefacts and in a manner that preserves information about physical properties – which in turn yields critical information about protein interactions. This means that you can assess if a peptide-based biotherapeutic is suddenly getting bigger, for example. If the biotherapeutic's size has changed substantially then it's likely to be binding to a target. You can also assess if this change in size is happening at specific concentrations. We can then look at the binding constant for this interaction and check if the stoichiometry data suggests the peptide is binding to one target or more and if one is being favored over the others – allowing you to spot different mechanisms of binding.

In other words, we are bringing scientists a step closer to being able to study notoriously difficult membrane proteins and intrinsically disordered proteins in as close to a native state as possible, by generating binding affinity and stoichiometry data in real time.

As a field, microfluidics is still growing – particularly in its application to analysis of proteins. Current systems are limited in what they can analyze; for example, we may only be able to separate a mixture based on a single characteristic. But, over time, I expect to see that changing, with microfluidic systems being used for more complex manipulations or separations that offer deeper insight.

One thing seems certain: with the right tools, researchers will be able to look beyond individual proteins – even beyond individual interactions. And if they can observe the rich interplay of the proteome, they are another step closer to developing a deep, system-wide understanding of biological complexity.

In turn, our ability to comprehend the full impact of perturbing these biological systems improves, which supports the development of more selective treatments.

Technology that allows us to explore proteins and antibodies binding and interacting with a host of other molecules with minimal interference helps unlock a deeper level of understanding. In turn, this may start to change the way we think about proteins – and biotherapeutics – altogether.

Reference

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Out With the Old and in With AI

Artificial Intelligence and other innovative technologies have the potential to disrupt every stage of the clinical trial process as we currently know it. It is high time we put these technologies to use.

By Chris Tackaberry, Co Founder and CEO of Clinithink.

Despite being vital to new drug development, the clinical trial process is broken. Patient recruitment and retention provide such significant challenges that their impact is felt industry wide. More than three-quarters of all clinical trials experience delays and with the daily bill for this somewhere between $600,000 and $8 million, the desire to find a more efficient method sits right at the top of the agenda. In addition to the astronomical costs, the stark reality is that these delays often slow down the entry of new medicines into the market, preventing patients from accessing new and innovative treatments. Even when patients are willing to participate, the hurdles are still significant; not least because the whole business of clinical trials is shrouded in mystery with very few people understanding or acknowledging the role they could play by participating.

As a highly regulated industry, the pharma market is often understandably cautious of change and, as a result, behaves relatively conservatively. AI and other innovative technology applications have the potential to disrupt every stage of the clinical trial process from matching eligible patients to monitoring and data collection. Whereas, the traditional clinical trial process is inefficient, time-consuming and incredibly costly, with drug development taking an average of a decade and, often, costing billions of dollars. It is time we made changes.

A great deal of time (and budget) has been spent on the development and implementation of Electronic Medical Record (EMR) solutions. Clinicians are able to "code" the diagnoses relevant to the patient's care and this information can then be shared with other healthcare professionals. However, every diagnosis starts with a story – and this is why doctors write notes. Those notes are rich in detail around symptoms, relevant previous history, impressions and ideas about what might be wrong and plans to investigate and treat. This documentation process is an essential step for the physician as s/he organizes their thinking and decides what to do next. An enormous amount of useful insight lives within these notes but, from an EMR search perspective, they are unstructured and therefore impossible to automatically "read" and interpret. Today, that work is done manually by human researchers.

By searching this narrative data using AI, clinical trial recruitment, for example, can be significantly enhanced. AI-driven software can dramatically reduce the time and investment currently required to find and enrol patients into clinical trials. By quickly and efficiently processing large volumes of existing unstructured patient data, sites are able to identify eligible subjects against trial-specific inclusion and exclusion criteria more quickly than reviewing patient data manually.

There has been a great deal of interest and enthusiasm for these types of technologies but as with any disruptive platform, it takes time for people to adjust and fully realize the benefits. However, even in the somewhat conservative pharma industry, there is a general consensus that change is on the horizon, so the adoption of such technologies is accelerating and outpacing the usual rate of change.

While AI is unlikely, at least in the short term, to replace conventional clinical trials processes in their entirety, it can remove some of the more repetitive or tedious tasks experienced by physicians and research nurses, promoting improved patient participation. There are many different creative streams in AI currently being explored and it is an incredibly exciting area to be involved in. There is no doubt that AI offers enormous opportunity, not only in clinical trials but also in clinical practice.

This in turn will expedite drug development and also change the shape of what we understand about disease and how we diagnose it. All to the benefit of the patient.

Celebrating PVP in Pharma

PVP has a long pedigree of use in both medicinal and pharma applications – and with innovations continuing to emerge, its use shows no sign of slowing down.

Dr Krizia M Karry's pharma career began over a decade ago in Puerto Rico. Despite initially focusing on PAT applications, process development and tech transfer, today she is fascinated by the use of excipients in the industry and works as a Global Technical Marketing Manager for Pharma Solutions, at BASF. Here, Dr Karry explains what led her to join BASF and the lessons she has learned about one of the industry's most popular excipients: PVP.

How did you join BASF?

After several years in the industry I decided to pursue graduate studies in the US. I focused my thesis on pharma challenges at the time: formulation and process design for poorly soluble compounds, and multipurpose manufacturing platforms for different types of dosage forms.

As soon as I graduated, I returned to the pharma industry where, in collaboration with R&D scientists, I scaled-up, transferred and validated processes for manufacturing tablets via high shear wet granulation, roller compaction, fluid bed coating and continuous manufacturing platforms. Interestingly, irrespective of the processing platform, one thing was clear: despite being the most crucial part of a pharmaceutical product, raw materials were the least understood systems! In realizing this I decided to join BASF, a technically-driven excipient manufacturer that is resourceful in generating a body of knowledge on its excipients to then share with its customers, my "previous" pharma peers.

What is the story behind the use of PVP in the pharma industry?

The PVP history is one that we are proud of at BASF. More than 80 years ago, the chemists of our Ludwigshafen plant in Germany mastered acetylene-chemistry to produce – in just five steps – a new monomer called N-vinylpyrrolidone. According to a 1939 patent by BASF chemist Walter Reppe, vinyl pyrrolidone reacted in the presence of catalysts to form the polymer we now know as poly vinylpyrrolidone – or PVP. This initial application data regarded PVP as an additive in the textile industry due to its great affinity to dyes, and as a binder and thickening agent.

During this same time (1940s), the Second World War was ramping up and access to blood plasma in Germany was extremely difficult. Critically wounded soldiers were treated with blood plasma to maintain the body's blood volume and minimize the chances of going into shock due to low blood pressure. By the end of 1940, BASF's Kollidon® PVP gained its first medicinal application as a synthetic blood plasma substitute. Its use was simple: Kollidon® was combined with water and inorganic salts and used in intravenous infusions. The higher the PVP content, the greater its efficacy in maintaining blood volume. The application was patented in 1941 by Walter Reppe and researchers from Bayer pharmacological laboratories.

In the subsequent years, PVP continued to gain interest in different fields and for a wide variety of applications due to its properties as a non-irritant, non-toxic, colorless, water-soluble polymer with excellent binding, wetting and film-forming properties. Today, PVP excipients are everywhere. In pharma, PVP is commonly used as a tablet binder, disintegrant, pore former and solubilizer.

In what way has PVP evolved over the years?

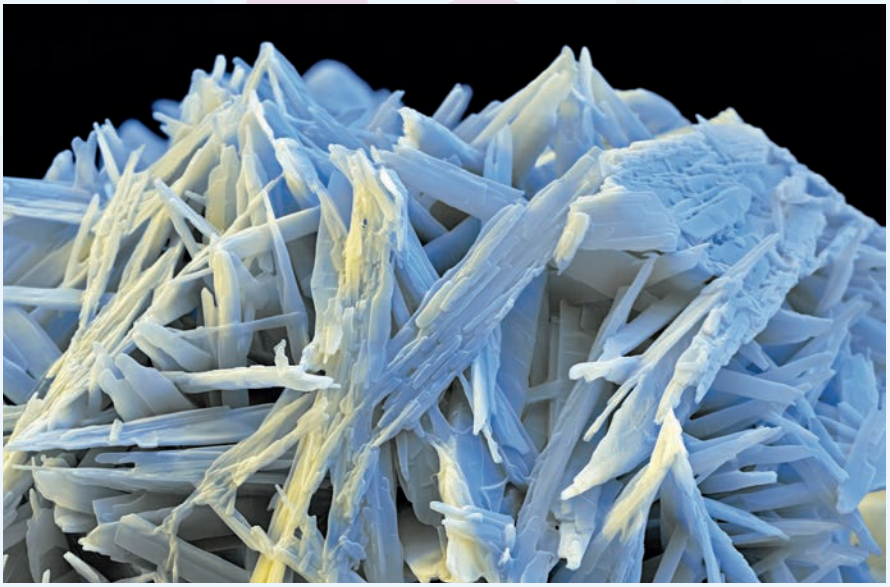
The hygroscopic properties of PVP have long been exploited in fluid bed and wet granulation processes for their correlation to high binding, wetting and granulating efficiencies. Moreover, PVP chemistry has evolved so that less hygroscopic copolymers are now available. For example, Kollidon® VA 64 and VA 64 Fine absorb three times less water than povidone at a given relative humidity whilst offering excellent dry binding properties – the latter being an excellent choice for roller compaction and direct compression continuous manufacturing applications.

As part of the PVP evolution, we have also considered the major oxidation impurities of the polymer (residual peroxides, formaldehyde and formic acid) and how to address our customers' needs in formulating oxygen-sensitive APIs. We have developed and introduced a low peroxide (LP) grade, Kollidon® 30 LP, that contains a sulphite-based antioxidant. Additionally, this product, as well as other PVP grades, are packaged employing BASF's patented PeroXeal® packaging. This packaging concept is another option we offer for further reducing peroxide formation in APIs and drug products. It is based on a combination of several components: an oxygen-impermeable inner liner, and a filling process under inert conditions. The result is a significantly lower risk of oxidation that allowed BASF to extend the shelf life of its PVP grades for up to four years for products that come with the PeroXeal® packaging.

What do you think have been the most important PVP products to emerge?

Kollidon® 30 is still one of the most important products in our PVP portfolio – and I believe it will remain a standard excipient in the formulator's toolbox because of its excellent processability, long shelf life and amenability to almost all processing platforms.

We have also seen a growing interest in crospovidone (Kollidon® CL grades) as the "superdisintegrant" of choice for tablet applications, as well as more recently as a "binding disintegrant". As a binding disintegrant, we found that tablet strength was inversely correlated with crospovidone particle size in formulations containing both



crospovidone and cellulose components, but formulations containing mainly brittle ingredients, allowed a proper binding of crospovidone during tabletting. As a result, tablet strength became less affected by the particle size of crospovidone.

We have developed a unique portfolio of crospovidones, covering both monograph type A and B as well as different applications: crospovidone type A Kollidon® CL, the standard superdisintegrant and Kollidon® CL-F with a finer particle size for improved tablet strength and surface quality; and the type B products Kollidon® CL-SF and Kollidon® CL-M – the SF grade being the ideal disintegrant for orally disintegrating dosage forms as it provides a creamy mouth feel rather than having a gritty texture due to its super-fine particle size, and the M grade as a micronized product suitable for roller compaction, and as a suspension stabilizer and pore former in sustained release applications.

PVP is not the only formulation option available. Why would formulators choose PVP over different options?

PVP has a proven track record in the pharma industry as a safe, multi-functional excipient. Specifically, its excellent solubility in water and other solvents make it a versatile excipient for almost all dosage forms, including wet granulation for solids production, solutions, syrups, injectables, and topicals. Its wetting and binding powers are an advantage for wet granulation, dry granulation and tabletting operations as they lead to compacts with higher tensile strengths. At the same time, its swelling properties make it an excellent tablet disintegrant even at very low concentrations. Its excellent film-forming properties can also be leveraged in coating formulations, oral films, ophthalmic solutions and flexible transdermal patches. And lastly, its chemical structure allows it to form chemical complexes with many APIs. This is leveraged by pharmaceutical formulators to improve drug solubility in liquid dosage forms (e.g., antibiotics), increase drug dissolution rate in oral dosage forms, and reduce drug toxicity (e.g., injectables and iodine).

How do you think PVP options will continue to expand in the future?

Solid oral dosage forms will remain the main driver for pharma developments and here PVP – soluble or insoluble – will continue to play an important role. However, we know that close to 70 percent of new molecular entities in pharma pipelines are poorly soluble compounds. To front this challenge, we are working closely with formulators to expand their toolboxes to include PVP copolymers (such as Kollidon® VA 64) that have high drug solubilization capacities and storage stabilities, and that are amenable to typical solid dispersion processing methods, such as hot-melt extrusion and spray drying.

In the future, I believe excipient options will also continue to grow. Despite the widespread use of excipients across numerous industries, they are oftentimes one of the least understood systems. In working in the pharmaceutical industry and now at BASF, I see we continue asking the same questions, such as which parameters should be used to properly characterize electrostatics and flowability, and what raw material properties are relevant for continuous manufacturing. By working together and sharing knowledge around excipients, we can finally answer these questions and design excipients that are "fit-for-use". These partnerships will certainly give manufacturers the confidence they need to use newer excipients.

IT'S A KIND OF (FORMULATION) MAGIC

Meet the grand winner of The Medicine Maker 2018 Innovation Awards: Zydis Ultra, an orally disintegrating tablet made using resonance acoustic mixing that aims to boost patient compliance and acceptability.

By Stephanie Sutton

Zydis technology – the first orally disintegrating tablet (ODT) – was commercially developed by Catalent in the 1980s. As the name suggests, such tablets are specifically designed to disintegrate when they come into contact with saliva, to enable swallowing without chewing or the need for water. FDA guidelines state that ODTs should disperse in less than 30 seconds. Zydis ODT is made using a lyophilization process that results in extremely rapid disintegration – as fast as three seconds, once the dosage form is placed on the tongue. The drug is presented in a finely dispersed form for rapid onset, and depending on its specific properties, may be absorbed from the oral cavity and avoid first pass metabolism in the liver.

"Zydis ODT was the first orally disintegrating tablet. Before that, there were chewable tablets, capsules, and lozenges, but no solid dose that disintegrated instantaneously in saliva, with minimal patient input. The only alternative at the time was a suspension or liquid product, but these can be very inconvenient to take and come with concerns around the accuracy of dosing," explains Ralph Gosden, Head of Product Development at Catalent.

"After the launch of Zydis ODT, other products began to emerge to try and match the performance using different approaches, such as compressed tablets incorporating high levels of disintegrating agents," says Rob Smith, Vice President, Product Development and General Manager for Catalent's early development site in Nottingham, UK. "You can create an ODT in a variety of different ways, but some of the tablets produced had very slow disintegration times, which is why the FDA deemed it necessary to issue guidelines around ODTs in 2008, to clarify the expectations of ODTs. In some products, disintegration time was over a minute."

As well as a disintegration time of less than 30 seconds, the FDA guidance encourages manufacturers to also

consider tablet size and weight; an ODT that is too large or that disintegrates too slowly could be a choking hazard. The guidance states (1), "While tablet size or weight is not explicitly included in the definition, you should consider the effect large tablets have on patient safety and compliance. We generally recommend that the weight of the tablet not exceed 500 mg; however, if a tablet intended for use as an ODT weighs more than 500 mg, its ability to perform effectively as an ODT should be justified based on product performance. For such products, the extent of component solubility (e.g. tablet residue, need for liquids) can influence the acceptability of the product being labelled as an ODT."

PATIENTS IN MIND

Oral drug delivery is well-recognized as a convenient, economical and safe route of administration. And much has been written about the specific advantages of ODTs (2,3). From a patient perspective, ODTs offer the convenience of medication "on the go" and without water – which is particularly useful for certain medical conditions, such as a migraine which can hit unexpectedly, and where there is no access to water. And if a patient feels nauseous, as with motion sickness, consumption of any liquid may be best avoided. Of course, there are also people who just do not like swallowing tablets at all.

"Sometimes the barrier is psychological, but in other cases the ability to swallow may be severely hindered by age or a medical condition – consider an elderly patient with dysphagia, for example, and the fact that many geriatric patients are taking multiple tablets per day," says Smith. "Swallowing tablets or liquid suspensions can also be an issue for very young pediatric patients and there are particular concerns about the dosing when children spit out their medicines." Studies have shown that ODTs are particularly popular for pediatric patients, with many medical practitioners believing that liquids (the most common type of dosage form for children) could be replaced by ODTs (4).

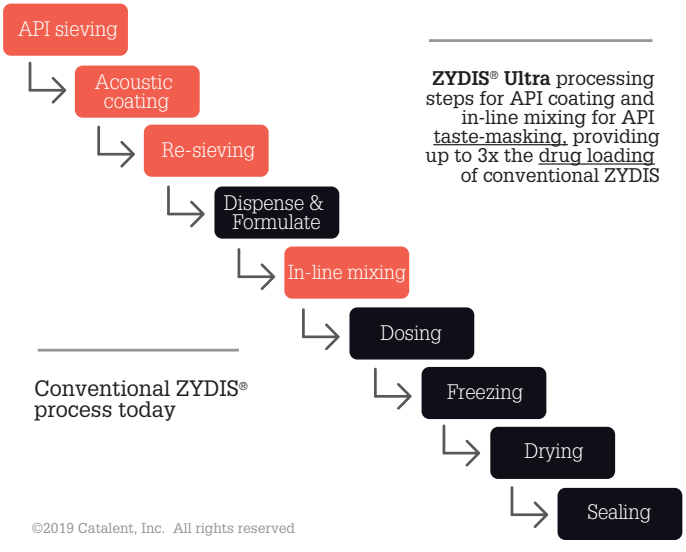
But there was also another driver for the development of the Zydis ODT technology: the continuing need for improved patient compliance. Poor compliance has been reported as one of the most common causes of nonresponse to medication. In some cases, the convenience of the dosage form could help encourage patients to take their medicine at the right time, but there are also patients who refuse to take medicine at all.

"The secret ingredient in Zydis Ultra ODT? It's a mixing process, which has been in development since around 2012 and uses resonant acoustic mixing."

"This is a common issue with psychiatric conditions, such as schizophrenia, depression, or bipolar disorder," says Smith. "Some patients require supervised administration to prevent them from regurgitating the medicine or hiding it – concealing a tablet in a cheek to eventually spit out is a common tactic adopted by some patients to avoid consumption. Once Zydis ODT is in the mouth, you can't spit it out because it disperses so quickly. Because of these advantages, it has been used for a range of medicines targeting psychiatric disorders and can even be employed for medicines designed to help heroin addicts."

Studies have also shown that nonadherent patients with schizophrenia or bipolar disorder treated with orodispersible formulations are less likely to be hospitalized or suffer relapse compared with those patients taking standard oral coated tablets (5). Other studies have shown that ODTs can improve patient compliance (6). "We've also conducted our own research and have found that ODTs can improve patient compliance – 98.5 percent compliance versus 81 percent compliance with a standard oral treatment," says Susan Banbury, Head of Zydis Formulation at Catalent (7).

From a business perspective, the team also believe that such unique dosage forms are harder – if not impossible – to counterfeit.



ZYDIS® Ultra processing steps for API coating and in-line mixing for API taste-masking, providing up to 3x the drug loading of conventional ZYDIS

Conventional ZYDIS® process today

MAKING THE MAGIC HAPPEN

A Zydis tablet is made using lyophilization. Firstly, the bulk API is formulated into a liquid solution or suspension. The liquid is then precisely filled into pre-formed blisters and passed through a cryogenic freezing process to control the size of the ice crystals, before the units are transferred to large-scale lyophilizers.

Given that tablets made by freeze-drying can be sensitive to environmental conditions, the sealing and packaging process is also important. The blisters are subject to a heat-seal process to protect the product from varying environmental conditions and to ensure long-term stability.

Zydis is also capable of delivering some proteins and peptides orally (Zydis Bio), as the drug has the potential to bypass the GI tract. The lyophilization based manufacturing process and its low temperatures reduces the potential for heat damage to the biologics, but the process requires careful formulation with the right selection of ingredients to optimize in-process stability.

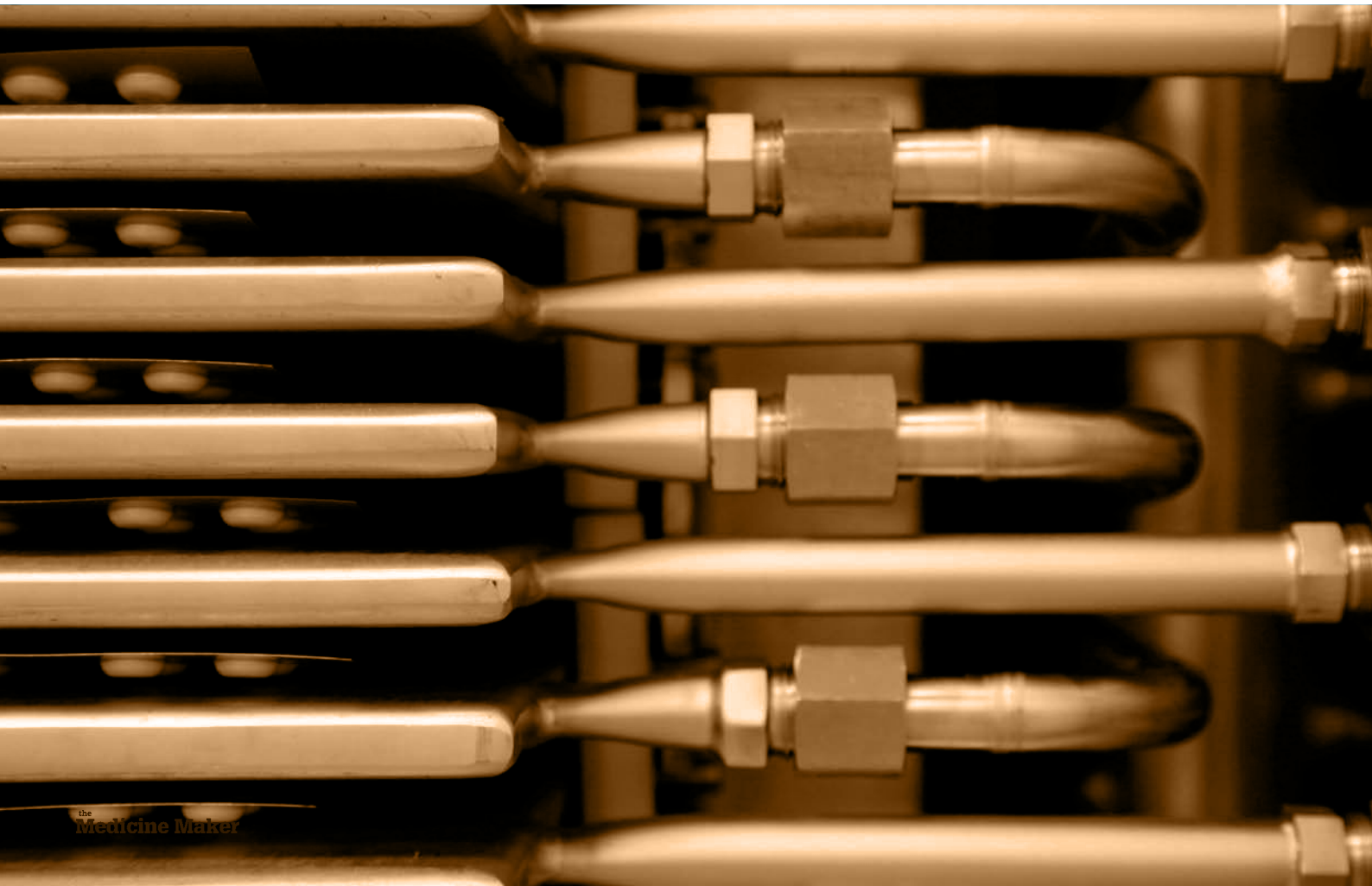
ULTRA NEW TRICKS

The first Zydis ODT to receive approval from the FDA was Claritin (loratadine) in December 1996, but today more than 30 products have been launched in 60 countries, including both prescription and over-the-counter medicines. Catalent manufactures over one billion Zydis ODTs every year in 17 different therapeutic areas. But if the first Zydis ODT was approved in the 1990s, then how did the latest iteration win The Medicine Maker Innovation Awards over 20 years later?

Although offering many advantages over other solid dosage forms, the original Zydis technology had some limitations with drug loading and taste-masking – with the latter being particularly important for a product dispersing in the mouth. And so, Catalent's research team worked on the next generation, called Zydis Ultra technology.

"There were taste-masking options for the conventional Zydis formulations, such as flavors and sweeteners, or by combining with an ion exchange resin or cyclodextrin. For some APIs, these strategies work well, but in other cases the effect was limited, or could not accommodate the required tablet dose. For example, in general, the more soluble the API, the higher the risk that the taste will be unacceptable," says Banbury. "Coated APIs for taste masking purposes have been available for some time. However, incorporating them into the conventional Zydis formulation using standard processing methods, while maintaining the integrity of the coat, was challenging. Zydis Ultra technology allows a coated API to be used. And drug loading is three to four times higher than with a conventional Zydis ODT."

During the formulation of any solid oral dosage form, the mixing process is crucial, with a potential impact on compression, dissolution and other finished product characteristics. Mixing can also be affected by conditions such as device capacity and product mass, so you need to choose the right technology to get the right outcome. The secret ingredient in Zydis Ultra ODT? It's a mixing process, which has been in development since around 2012 and uses resonant acoustic mixing technology to coat the API. "The technology was initially developed for the ammunition and ballistics industry, where it received a lot of



US federal investment. Zydis Ultra technology was made possible because of it," says Craig Scott, Director of Product Development at Catalent. "Resonant acoustic mixing works by controlling vibration through acceleration and frequency. The materials being mixed do not come into contact with any moving parts, with the exception of the vessel, so it's considered a safe process that generates no static."

Acoustic mixing can be used for dry mixing materials with various flow aids, but for Zydis Ultra ODT, the technology is used to form a continuous polymer layer around API particles, without solvents. "The easiest way to describe? It's like the materials are being forcibly shaken," explains Scott. "API particles are mixed with micronized polymer aggregates using an acoustic vibrator at a very high velocity. This creates a significant amount of energy (up to 100 times the force of gravity), which causes acceleration and collision of particles, and raises the temperature until the dry polymer becomes malleable and molds itself around the API in a very thin layer. No solvents are involved and the API retains 70 to 85 percent of its potency."

Resonant acoustic mixing can coat particles less than 100 µm with minimum impact on final particle size, whereas conventional coating typically results in significantly larger particles that can lead to a grittier mouthfeel in ODTs. Researchers at Catalent have been able to formulate both ibuprofen and acetaminophen using the new technology (3).

"We then formulate the coated API into a typical Zydis formulation so that it maintains its fast disintegration time. It took a lot of work to adapt and refine the approach from the ammunition industry and then scale it up to something that we could commercialize!" says Scott. "There's a huge amount of work involved when looking at the various different options – and one of our key goals was to ensure that the new formulation could be filled on our current existing lines. Our engineering and operations teams have had to work very closely together. The dosing, in particular, was a very big challenge."

For some extra help in adapting the technology, the company also approached the New Jersey Institute of Technology. The challenge was achieving a complete, perfect coating of the API particles so that there is negligible release of the API for the first 90 seconds, but that the material is then fully available for gastrointestinal absorption. "The team also had to address how we integrate a very delicately coated API particle into a liquid solution or suspension without

THE "WOW" EFFECT

"I was working for a competitor to Catalent when I was given a placebo of Zydis. I tried it and was so wowed by the technology that I decided I wanted to work for them. I quit my job, joined Catalent, and I haven't looked back! It's been rewarding to see the technology go from strength to strength, with Zydis Bio and now Zydis Ultra. In the future, I hope we can use the Zydis technology to deliver vaccines. The coating doesn't allow for the sublingual uptake that you would normally want with a vaccine, but we have a few tricks up our sleeve that I won't give away! I think Zydis has been a major breakthrough, shaking up the traditional platforms for oral solid dosage. Zydis Ultra has so much potential with the extra dose loading and I think it will fulfil more promises beyond what we've seen with Zydis." – *Rob Smith.*

"Working with a technology that genuinely meets the needs of specific patient groups has been a real pleasure. The needs of demographics who are often excluded (including pediatric and geriatric populations) are addressed in ways that simply cannot be achieved using conventional approaches. Zydis definitely has a "wow" effect when you first try it. I'm looking forward to getting this dosage form to more patients and indications with the release of Zydis Ultra." – *Susan Banbury.*

"It's a real privilege to work on a dosage form that you can really believe in. I've been working on Zydis for about 15 years and seeing it evolve over the years has been great. I still remember the feeling when I saw Zydis Ultra running down the commercial lines without any significant issues. It was great to know that we could really create this on a commercial scale! On a personal note, I have a young family. Administering medicine to children is difficult, especially when they spit out liquids, which ruins the dosing! When you give a young child an ODT, you know you have given them an accurate dose. I find that very comforting – both as a parent and as a developer. It also gives a positive medication experience to children." – *Craig Scott.*

> "Previous consumer preference studies with major pharma companies using a Zydis Ultra placebo garnered outstanding feedback."

damaging the coating while ensuring that the taste-masking characteristics are successfully maintained," says Smith. "We have some patents on this under submission, so in the future we'll be able to talk more freely about how we take these delicate API particles through the manufacturing process."

AND COMING UP NEXT…

According to the Catalent team, there has been considerable interest in Zydis Ultra, particularly for products that have known taste-masking issues. "We have four products in the pipeline at the moment. The first is planned for launch around 2021; we're ramping up to supply the bioequivalence studies at the moment," says Scott. "Clinical data is due back later this year, and we have also been conducting consumer preference studies. Our previous consumer preference studies with major pharma companies using a Zydis Ultra placebo garnered outstanding feedback. I like to think the outlook is positive!"

INNOVATION AWARDS 2019

Do you want to share the story behind your technology in a future issue of The Medicine Maker?
In our December 2019 issue, The Medicine Maker will showcase the top 15 technologies to have been released throughout 2019. The final winner will be decided by a public vote and – just like Catalent – will be able to tell the story behind their innovation in a 2020 issue of The Medicine Maker.

The nomination form for the 2019 Innovation Awards is now live: http://tmm.txp.to/innovations19-noms

The rules?
The technology must have been released (or planned for release) in 2019 and it must be expected to have a significant impact on drug development or manufacture.

The innovation can be a piece of equipment, IT software, formulation technology, drug delivery method or any other innovation that you think could fit the bill.

Questions?
Contact the editor: stephanie.sutton@texerepublishing.com.

And because of this outlook, Catalent announced a $27 million investment in March 2019 to help commercialize Zydis Ultra technology, given that a number of development programs are now reaching the full development stage. The Zydis development and manufacturing operation is located at the company's 250,000 square foot site in Swindon, UK.

Even with the additional opportunities available with Zydis Ultra, the original Zydis technology is here to stay, says Scott. "For some APIs, the original Zydis technology remains the most appropriate option, but Zydis Ultra builds on this expertise and in combination with the technology continues to go from strength to strength; I've been involved with Zydis for 15 years and this is the biggest development pipeline I've ever seen."

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Speed and Simplicity – A Formulator's Best Friend in Development

From core to coating, there is a lot to consider when it comes to developing and optimizing a solid dosage formulation. Simple best practices can offer an edge that allows formulators to reduce potential problems that could occur in later stage commercial manufacturing.

By Jayesh Parmar

Formulators are faced with many choices during the early phase of development, and they must focus on the project milestones they need to deliver. Examining formulation strategy early can deliver key benefits and having an end goal in mind early on leads to greater efficiency, as everyone will understand what they are working towards. Understanding the molecule is the first step, then exploring the needs and options for formulation enables development to progress faster and smoother.

Solubility is one issue that is often encountered with new molecules in development. Many technologies are available to help solubilize an API; however, if a robust formulation and process is not developed then it can impact the subsequent manufacturing of a consistent product. Using the right technology and choice of excipients, it's possible to develop a stable formulation with reduced complexity. Partnership with key suppliers of ingredients and equipment is critical during development phase. For example, formulators need to ensure that the process parameters for equipment used during development are transferrable to commercial-scale equipment. Similarly, formulators should partner with suppliers before putting in place any particular specifications for ingredients; thus avoiding future supply issues.

Formulation simplification

Designing the formulation for your next new product involves many decisions. What is the desired drug release profile? What excipients should be used? Do they interact with the API? Which film coating should be used? And how should the tablet design look? Drug developers also need to consider what will work at the commercial manufacturing scale. Generally, I recommend formulators to keep their strategy simple; by reducing ingredients and process steps this is less likely to cause problems and results in the most cost-effective option. From a regulatory standpoint, complex processes are also more likely to lead to complex questions from regulators and may extend the approval process.

"Designing the formulation for your next new product involves many decisions. What is the desired drug release profile? What excipients should be used? Do they interact with the API? Which film coating should be used? And how should the tablet design look?"

Process efficiency

In the very early stage of formulation, a capsule is generally the preferred oral dosage form, due to its binding capability for clinical trials. However, due to economic, ease of manufacturing and marketing considerations, most oral solid dosage forms on the market today are tablets. There can be a great opportunity for cost and time savings, as formulators can develop a dosage that works both in a capsule and as a final tablet form.

Direct compression is considered by many in the industry to be one of the simplest methods for manufacturing tablets and works well at large manufacturing scales. In comparison, wet granulation involves multiple steps and the use of moisture, which can introduce the risk that the API may degrade. With industry preference leaning towards direct compression, several excipients have been developed that excel in this area. As one example, consider our newest excipient, StarTab directly compressible starch. StarTab is designed specifically for direct compression and offers benefits in terms of both simplifying the formulation and processing. Starch excipients are commonplace in the industry, but many require additional ingredients to be fully effective in the formulation – such as an excipient to improve flow, an excipient to improve compressibility, as well as superdisintegrants. This can complicate the formulation and process, given that you need to examine how all of the excipients interact with one another, as well as interact with the API; lactose, for example, is one common formulation ingredient that can interact with certain types of API, so it is best avoided. StarTab is a single excipient which, because of its particle shape and

size, is directly compressible and provides improved flow during manufacture. It can also avoid the use of superdisintegrants – and be used at both small scale and large scale, as well as with the latest technology such as continuous processing. Excipients like this offer manufacturers significant flexibility in terms of how they manufacture their product.

Other excipients can help with productivity, such as METHOCEL DC2, which also enables manufacturers to replace costly wet granulation in matrix tablet production with more cost-effective dry granulation and direct compression techniques. It is a pure, compendial hypromellose (HPMC) and the most flowable direct compression grade of HPMC available today. It exhibits better flow in formulation blends compared to traditional hypromellose-based formulations, and uniform die-fill during tablet manufacturing provides tighter tablet weight control. Overall, it can improve process capability.

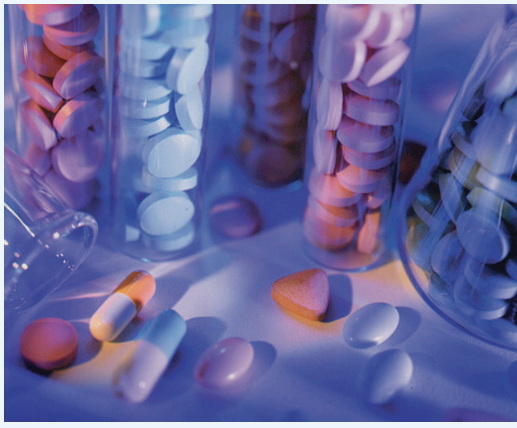
Another important formulation decision revolves around API stability, which can be improved through the correct choice of film coating. Whilst film coatings have an important role to play for aesthetic purposes by giving the tablet a perfect finish, they also play a part in defining branding strategies. They also fulfil more practical roles; a good coating protects the tablet during storage from moisture, light and oxygen, for example, and helps to stabilize the API. The right coating choice also enables ease of transition of drug production between manufacturing sites; in early stage development the final site(s) for manufacture is not usually a consideration. Colorcon's Opadry QX has a wide processing latitude which means it is suitable for use across a range of coating equipment – which is imperative if you don't know where the final product will ultimately be manufactured. Specialist film coatings also provide a barrier that reduces the ingress of moisture to the tablet core, helping to support stability for sensitive actives. And lets not forget, film coating also helps tablets to run smoother in tabletting equipment and protects them from damage during the manufacturing process.

Right first time

Failing to consider core and coating formulation early on can lead to delays, added costs and, in the worst-case scenario, project termination. Often, big pharma companies understand the benefits of investing in early formulation and will have large departments dedicated to this role, but many others, particularly small and medium-size companies, may not have the resources and, understandably, will be prioritizing proving efficacy and safety of the API. In many instances, rather than developing an optimized formulation strategy, a company will simply resort to the same tried and tested approach that they have used for their previous products, even though it might not be best matched with the newest molecule. At other times, a company may want to take a new approach to optimize the formulation but struggle to find a starting point, since there are many options!

Companies do not need to go through the formulation process alone; Colorcon offers its HyperStart starting formulation service globally to help bench scientists understand the options available for delivering their API to the patient. We simply take basic information (confidentially, of course) related to the API, such as solubility, the dosage, and the technology being considered for the final dosage form, and then deliver back a starting formulation. Some companies already have good starting guidelines in this area, but what worked for one formulation may not be the best starting point for the next. Our service supports scientists to make decisions early, giving them an informed starting point.

In my view, vendors have an obligation to support on the regulatory side too with documentation. When it comes to excipients and ingredients, it can be surprising how regulations across the world differ; what is allowed in the US may not be allowed in Japan, for example. This can also apply to certain pigments – and it wouldn't be the first time I've come across a company shocked to learn that their manufactured tablet in one country can't be marketed in another without changing the ingredients! Having this information early allows you to plan early and choose ingredients accepted in all the countries you are targeting for market launch.



Although attrition in drug development is high, considering the formulation in the early development stages will definitely lay the foundations to support clinical success, and good formulation expertise can make all the difference.

Jayesh Parmar is General Manager at Colorcon.

NextGen

R&D pipeline
New technology
Future trends

A Continuous Cycle of Success

Helping to meet demands and reduce shortages... Is continuous manufacturing the way forward for pharma?

By David Thompson

April 2019 marked the end of Scott Gottlieb's highly active tenure as FDA Commissioner. Throughout his time in the role, he made it explicitly clear that continuous manufacturing (CM) was a key factor in supporting innovation and "modernizing the pharmaceutical industry" (1). The call has been echoed by many others within the FDA – and elsewhere in the industry too. Pharma companies, however, have been slow to leave batch manufacture behind. Four years ago, only one drug made with CM had been approved and the situation hasn't improved much since; today, there are around five products approved by the FDA made using CM.

CM undoubtedly requires manufacturers to have a certain level of front-end knowledge in terms of the management of procedures that will result in a successful product launch. Transient solid formation in a batch reactor, for example, is hardly a cause for concern, as the mixture can simply be stirred and eventually the solid should redissolve. But when such a solid forms in a flow process, new challenges arise and manufacturers face delays as they attempt to unfoul their reactors and/or manage the shutdown and cleaning of their systems.

Once these types of teething issues are addressed, however, there are huge benefits to CM. The current batch manufacturing process is costly and lacks flexibility. With a smaller physical footprint, CM enables CMOs and other manufacturers, in principle, to produce final drug products seamlessly in a GMP compliant manner. To date, pharma companies seem more likely to accept CM in regard to tabletting – a low bar for the industry given that many tableting machines already run continuously. I firmly believe that more research effort is needed to

"I firmly believe that more research effort is needed to improve CM for the development and manufacture of drug substances to de-risk this promising approach and enable broader adoption in the pharmaceutical industry."

improve CM for the development and manufacture of drug substances to de-risk this promising approach and enable broader adoption in the pharmaceutical industry. I've heard from many people that although there is strong interest in this area, many projects taking place in companies are running as skunkworks until decision makers can be convinced that it's worth the investment. It's also well known that in a highly regulated industry like pharma, it can be difficult and risky to change the manufacturing process for already marketed products. Consequently, it's clear to me that CM will be more applicable to new chemical entities coming through the pipelines and for generics where the cost of production can be lowered.

It is highly encouraging that the FDA is keen to help companies implement a more continuous form of manufacture into their practice. In February of this year, the agency issued a draft policy that detailed the development and implementation of CM for brand, generic and over-the-counter drugs. It charged its Emerging Technologies Team with the task of aiding early CM adopters with resolving "implementation challenges and navigating the application review process for products made with these modern methods" (1).

Make it work

At Purdue, I am a Professor of Organic Chemistry and my main focus is on drug delivery – designing different kinds of materials that respond to different metabolic conditions to release their drug cargo. It's very much based on fundamental chemical principles wherein you need to learn about the local environment where you want the drug to be delivered, and then design a material that responds to those conditions. For years, my group and I have focused on the use of microfluidic synthesis of particles for drug delivery. In many cases, the novel synthetic materials we made were mixed via microfluidic devices. As part of this work, we learned to precisely control the size of nanoparticles and designed continuous processes for preparing broadly different classes of nanoparticle assemblies. Since then, we've pivoted to also apply continuous synthesis

approaches to the telescoped preparation of small molecule APIs.

As part of a Defense Advanced Research Projects Agency (DARPA) funded project called Make-It (a program designed to help automate small molecule discovery and synthesis), my colleagues and I developed a cost-effective, time-efficient CM method for the manufacture of lomustine (2). Lomustine is a chemotherapeutic used in the treatment of glioma, melanoma, lung cancer and lymphoma.

For Make-It, DARPA envisioned a system that could use artificial intelligence to plan and optimize synthesis routes, and interconnected fluidic modules for continuous synthesis – including algorithms for automation and process control, and in-line characterization and purification (3). Ideally, an individual would be able to request a molecular structure and the system would find out the best method to synthesize the molecule and scale up to tonnes per year routes, and conduct the formulation and tableting. It was very ambitious. Because of the production rates that were called for – and the fact that the desired target small molecules listed by DARPA were multiple step reactions – it was clear that a continuous process would be needed to achieve the desired throughput.

We were inspired to focus on the production of lomustine after reading an article written by Henry Friedman, a neurooncologist at Duke University, in The Cancer Letter. The article explained that the price of the generic therapeutic had increased by 700 percent between 2012 and 2017, despite the fact that each year in the US, 33,000 new cases of lymphoma are diagnosed. Today, the price increase has reached 1400 percent. Consequently, some patients are being priced out of their medication and others are left with the difficult decision of reducing their doses.

DARPA actually provided a list of targets for the Make-It program – and lomustine was not on that list. But in time they enabled our group to expand the focus. At the same time, they also de-emphasized the formulation and tableting aspect of the project. It struck us that if we were able to produce lomustine through CM, we would be able to illustrate the power of a continuous process in catering to the needs of patients marginalized by the ever-growing prices of drugs. We've actually looked at four compounds: diphenhydramine, Atropine, diazepam and lomustine – the equipment was the same for all four, underscoring just how flexible CM technology can be.

I assigned one of the students in my lab, Zinia Jaman, to develop a continuous synthesis for lomustine in February 2018. By August 2018, she had created a CM process that produced a highly pure product (higher than the commercial

"We were inspired to focus on the production of lomustine after reading an article written by Henry Friedman, a neurooncologist at Duke University, in The Cancer Letter."

substance) with an overall yield of 63 percent and a residence time (the average length of time to produce the entity end-to-end) of nine minutes. The lomustine was prepared using two separate telescoped flow reactors in a linear sequence. This microfluidic approach was selected for its ability to radically reduce the cost of manufacture and make use of inexpensive starting materials. Most profoundly, the production rate was approximately 110 mg per hour using two coupled reactors the size of a microscope slide. I think this really highlights the power of CM. We can produce a much-needed medicine in a very cost-effective way – and Zinia was able to design this process relatively quickly!

And why stop at lomustine? The approach can also be applied to the production of other medicines, giving us and others within the industry the opportunity to more thoroughly address patients across disease indications.

A Based on our work, we have created a company called Continuity Pharma that aims to develop GMP continuous processes for different APIs. Once our milestones are met, I hope we'll be able to help with one of the biggest issues affecting drug development – and the more we can showcase the advantages of CM, the more we expect the industry as a whole to seize the opportunities that it can so readily provide.

We are also helping colleagues in academia who have interesting drug leads that they need to scale up. It's not difficult for medicinal chemistry researchers to make enough drug product for mouse studies, but as soon as they progress to follow-up studies on promising leads in larger animals, they need more compound – and many labs aren't set up for this. We've started working with colleagues to scale up their synthesis via a continuous approach to support the progression of these leads through the developmental pipeline.

Counting the benefits

I think the research from my group demonstrates how nimble academia can be when embracing CM and we have begun thinking more broadly about the real-world use of this technology. We can't say right now what the price will be for CM-derived lomustine because, although we've costed the raw materials (around $5 per gram), we haven't taken into account other elements such as hardware, maintenance, and personnel costs. And the real benefit of CM lies not necessarily in cost, but in production agility. Consider the fact that the output of conventional batch processes leads to the generation of huge quantities of drug intermediates and products that then sit in warehouses waiting to be shipped to the next unit or formulator, leading to an unnecessarily expensive use of capital. For some drugs, this can be a huge problem since not all APIs can be stored for long periods of time without degrading. Being able to produce a drug product just before it is shipped would ultimately enable us and others to improve drug quality and deploy resources more effectively.

The industry is still finding its feet when it comes to CM, but I believe that we will inevitably become more reliant on continuous processes. There is increasing pressure on drug prices and a greater desire for local facilities. Additionally, I think both industry and consumers are becoming increasingly aware of the environmental costs of drug manufacture, particularly with respect to energy consumption and waste generation. Continuous processing allows for high throughput manufacturing in a very small footprint. There is also a lot of discussion about the "ballroom concept" for manufacturing – that is, a large manufacturing area with no fixed equipment, allowing for increased flexibility and plug-and-play functionality. It also reduces the costs of construction associated with multi-story facilities that harbor large reactors.

CM will not replace batch manufacturing practices. Batch allows for high levels of quality control and the ability to modify it to suit company needs allow it to remain an attractive option for manufacturers. But, as CM gains more traction it should be able to work harmoniously alongside more conventional processing approaches.

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What's Beyond the Bioprocess Automation Starting Line?

The Internet of Things and robotics are already the working standard in fast-adapting industries. Now, these technologies are (conservatively) making inroads into the biopharma industry. Here, we consider what comes next – and assess whether the benefits outweigh the risks.

By Svea Grieb, Kai Touw and Dan Kopec

Automation drives the production of higher quality and more consistent biologic drugs and regenerative therapies at reduced costs of goods (CoGS) – and with higher flexibility and faster time to market (1, 2). And when it comes to automation of bioprocesses, process analytical technology (PAT) and advanced data analytics are crucial enablers because of the need to measure critical process parameters at all stages.

The main advantages of bioprocess automation can be summarized as:

- Consistency in product quality and quantity; variations of critical process parameters (CPPs) are reduced and process robustness is increased (see Figure 1).
- Fast and predictive up- and down-scaling; a well characterized and monitored process alongside scalable hardware significantly reduces the cost and effort of scaling, as variations can be accounted for in an automated and predictive fashion.
- Reduced risk of lost batches and increased process safety; operator errors and contamination through manual sampling are reduced. The timely identification and correction of process irregularities reduces the risk of lost batches.
- Operators are free to work on tasks that cannot be (easily) automated.
- Cell variation arising from different sources – as could be expected from different patients in personalized medicine – can be managed through a process that is flexible and able to dynamically adjust to wide variations – through PAT – to assure high process consistency irrespective of the starting material.

There are a number of key technologies that will help the industry to achieve more automated processes. For example, we believe that spectroscopic techniques will become more abundant in both upstream and downstream bioprocessing because they can be used to perform label-free, online measurements of several analytes, cell properties and product quality attributes – and replace offline measurements during the bioprocess. We envision the use of a combination of different spectroscopic techniques, including NIR, Raman and UV-Vis, to achieve online measurements. That said, there will also be a continuing need to use and further develop other technologies, such as sensors for bio-capacitance and tools for the measurement of nutrients/metabolites; here, spectroscopy cannot provide solutions. To propagate the use of spectroscopy in GMP, biomanufacturers will need a combination of measurement technologies that can act as cross checks.

Advanced data analytics must come hand in hand with the application of sophisticated PAT tools. Together, they can have a high impact on commercial processing because measurements can be moved forward in the process to the point of controllability. By using process fingerprints, the state of the process can be assessed at any time. Furthermore, through real-time univariate and multivariate process monitoring, data can be used to simulate and model process design and control – and ultimately lead to prescriptive analytics of product quality.

We also believe that flexible, automated skids are an important technological development, particularly for downstream processes. Flexible, automated skids, capable of handling different types of unit operations, all based on S88 compliant recipes (AINSI/ISA-88 is a standard addressing batch process control) would make it possible to run standardized and automated processes in facilities using the "ballroom" concept.

Solutions but also challenges

When discussing the automation of bioprocessing, we also need to evaluate technical feasibility and consider a cost–benefit analysis. And there are also regulatory, logistics and safety issues that need to be solved before automation can really be adopted widely in the biopharma industry. Though there are few applications in the process of biopharmaceutical drug production that would not benefit from automation, we do not envision a high degree of automation added into existing pipelines; for example, well-established fed-batch processes. Unless, of course, the automation adds a significant improvement to the process – as we have seen for automated temperature shifts at a certain viable cell density. Other processes may not benefit sufficiently from automation to

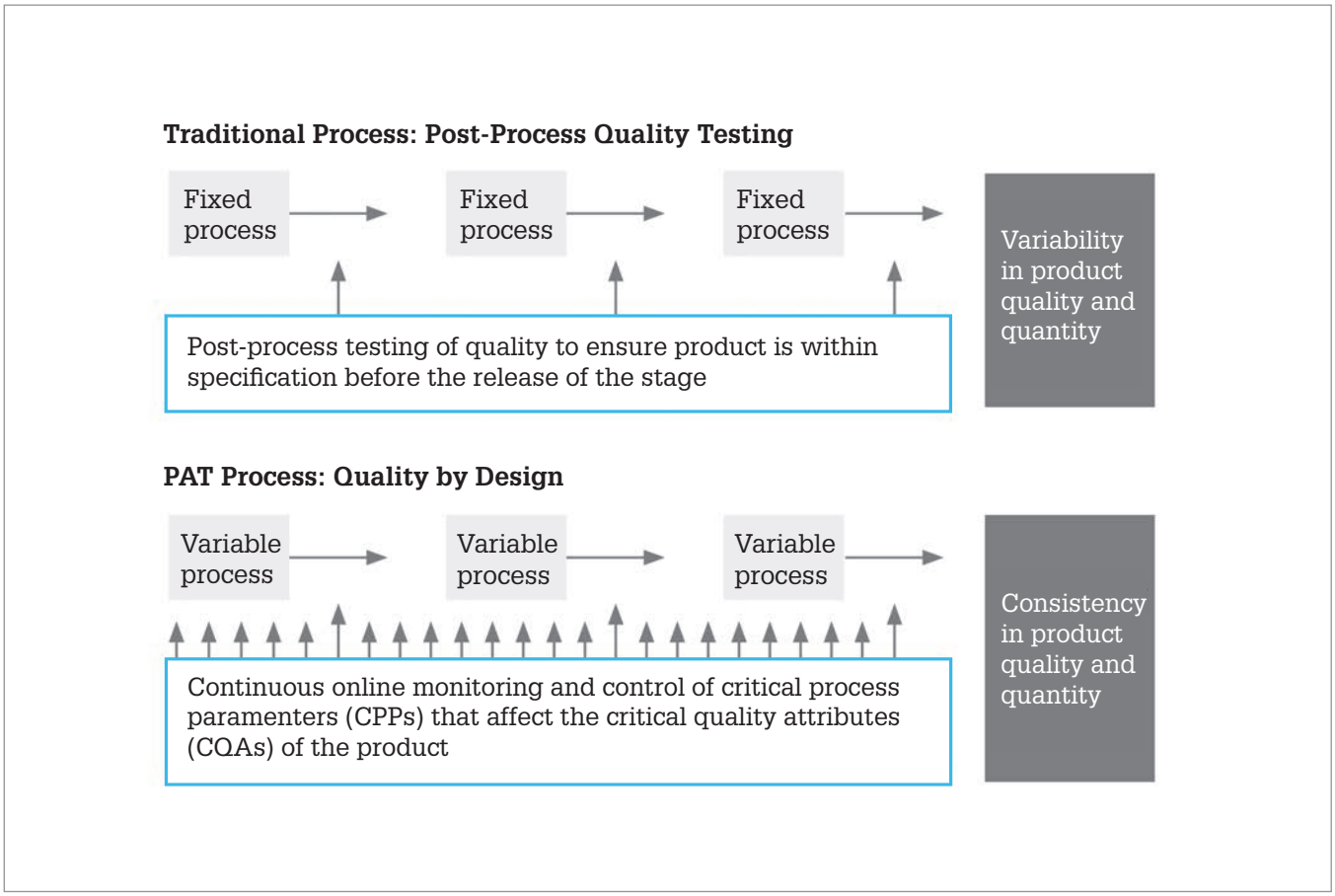

Figure 1: The traditional process and the PAT process.

warrant a change – perhaps areas where manual interference is already limited; for example, dead-end filtration. Finally, there are also processes that will be challenging to automate – product quantification of a target protein with a background of many other host cell proteins could be one such example.

There may also be compatibility and infrastructure challenges. The seamless integration of process equipment and process skids into an automated process, especially when considering flexible manufacturing facilities, is an issue. Communication between competitor solutions is not always guaranteed – an issue of insufficient established standards. Another challenge is presented when aligning the process automation concept of a supplier to the facility automation concept in terms of environmental monitoring, building monitoring and the required level of integration into resource planning systems.

And let's not forget regulatory challenges. Some concepts of modern automation technologies and sensor technologies are not yet covered by regulatory guidelines. The latter issue is especially true for multivariate data analysis, which takes all available data and integrates them into a fingerprint. The adoption of such batch fingerprinting concepts needs to be considered by regulatory bodies. The same questions arise for multi-analyte sensors that are based on computational AI models – as is the case with spectroscopy, for example. How do we validate a model for the use of GMP? What are the characteristics of a "good and robust" model? We should also consider the definition of "a batch" for continuous processing. Regulations that were initially established for a two-week batch process have to be adjusted to processes that can potentially run for months without interruption. Regulatory agencies are well aware of the challenges that come with modernizing the industry, but are open and cooperative to new concepts coming from technical advances in the

"When considering greater use of data, companies must also consider concerns around IT and data integrity."

field of automation, PAT and advanced analytics, as evidenced by the creation of the FDA's Emerging Technology Program (3, 4).

When considering greater use of data, companies must also consider concerns around IT and data integrity. A comprehensive automation strategy for an entire bioprocess, and potentially an entire production site, requires connectivity of all components and a centralized control unit. However, this requires data sharing and access that implies safety risks. We experience reluctance among our customers to adopt new technologies, such as cloud computing and wireless communication of PAT components. And we are convinced that the task of meeting the requirements of next generation manufacturing in terms of hardware, software, data analytics and infrastructure are too demanding and complex to be addressed by just one supplier. To overcome these challenges and to guide developments, we need the collaboration of several industries and a frank and open dialogue with customers.

Change is coming...

In the near future, we expect to see wider adoption of analytics in GMP, such as spectroscopy for metabolite control and bio-capacitance for viable biomass. We also foresee that multivariate data analysis (MVDA) and design of experiments (DOE) will be adopted by more users. Greater standardization will allow a real "plug and produce" scenario in a (multi-product) facility setup. And the field of hybrid modeling, where statistical and deterministic modeling principles are combined, will advance within the

Areas to Watch

We expect the upstream processes to benefit the most from automation, due to the highly variable nature of the biological process. A higher degree of automation and standardization of process steps will lead to improved batch-to-batch consistency and, in turn, product quality. There are perhaps three application areas that stand to benefit the most from automation and drive the development of PAT integration and advanced data analytics.

- Intensified/continuous processing. Intensified/continuous bioprocessing is a very hot topic in the biopharma industry because it increases the productivity of single-use (SU) facilities, while decreasing the manufacturing footprint (1). Such a boost to productivity renders SU facilities competitive to conventional stainless steel plants for the commercial supply of biopharmaceutical drugs. However, intensified processes are much more complex than conventional fed-batch processes and require tighter monitoring and control. PAT and automation not only provide this, but also reduce complexity for the operator. Intensified/continuous processing is likely to drive novel solutions for another reason: establishing new manufacturing pipelines with unique requirements justifies the cost and effort of going through the approval process for commercial manufacturing.
- Viral processes. When producing viral vectors for novel vaccines or gene therapy, the product is no longer a well-characterized molecule, such as a monoclonal antibody, but a complex of various proteins, DNA, RNA and in some cases lipid membranes. Such complexity makes it hard to identify and understand the factors influencing the product critical quality attributes. Hence, these processes benefit from a stricter control strategy, where high levels of automation and implementation of PAT and advanced data analytics play a key role. Another crucial aspect to consider when setting up a viral vector production process is operator safety. Using PAT and automation minimizes the need of manual sampling and off-line monitoring, hence reducing the risks of spills or leakages.
- Cell therapy. In personalized medicine applications, every process is inherently unique; the starting material is the patient's cells, so there is naturally high variation. Furthermore, these processes run at very small scales, with significantly high costs per batch and associated high risks (2). In these cases, lost batches must be prevented in any way possible. Online sensors for monitoring and control are able to reduce the contamination risk of manual sampling and account for process variabilities. Because of the small batch size, such processes will also greatly benefit from parallelization, where a refined automation concept is crucial to reduce CoGs and enhance patient safety. Advanced data analytics in CAR-T processes, for example, can improve process robustness by controlling the quality of viral vectors and accounting for intrinsic variation in raw material attributes and their effect on patient response.

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"We expect that modern facilities will apply intensified and continuous processing with advanced automation."

biopharmaceutical industry, further improving process understanding and simulation. Within systems biology, for example, these approaches are starting to be applied to enhance the production of cell lines commonly used in biopharmaceutical processing in a pragmatic way (5,6).

Five years from now?

We expect that modern facilities will apply intensified and continuous processing with advanced automation. They will be using state-of-the-art automated process batch management and S88 compliant batch recipe control functionalities, as well as plantwide visualization and electronic batch records. Furthermore, sophisticated analysis tools, such as HPLC and mass spectrometry, will be automated and integrated into the bioprocess. Together with an increased use of data science, quality-by-design approaches can be applied, allowing real-time release testing of product quality based on batch fingerprinting. Robotics will take over tasks, which cannot be automated otherwise, such transporting materials to and from the production location.

Ten years from now?

The far-future vision is highly influenced by the Industry 4.0 approach and related concepts, such as machine learning and the Internet of Things. We will see a fully automated, continuous bioprocessing pipelines that require no operator interventions. Processes can be monitored and controlled remotely. Every process will have a digital twin that can be used for process simulation and prediction. More and different data will be gathered and will reside in the cloud, where data analytics can be applied easily to improve processes, regardless of manufacturing location.

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Standardizing Single-Use

How can we reduce process risk and development times, streamline supply chains, lower costs and improve quality? The short answer: the standardization of single-use processing equipment – but end-users, suppliers and industry organizations must all work together to make that happen.

By Hélène Pora, Vice President Technical Communication & Regulatory Strategy, Pall Biotech

Single-use processing equipment now dominates pre-commercial biomanufacturing and is becoming an increasingly popular option at the commercial scale. The benefits are clear: pre-sterilized single-use systems can reduce setup and changeover times, while eliminating the costs associated with cleaning and its validation and they are associated with a high degree of flexibility to accelerate time to market. As demand for single use has grown, so too has the number of single-use systems on the market – with a wide variety of components, consumables and sensors. But the proliferation of choice has also led to a need for some degree of standardization. This question is more difficult than it first appears, as there many interpretations of what standardization really means in the world of single-use technology.

Single-use systems contain tubes, bags and filters, and different vendors will use different types of materials of construction for their components. The lack of standardization means that end-users may have to go through complex validation testing protocols for the combination of components they use. To complicate matters further, biopharmaceutical manufacturers often use different single-use systems and components, in different combinations, at different sites – or even within the same site at separate buildings. And that can make extractables and leachables studies complex and expensive.

A degree of standardization would reduce the risk inherent in the process, streamline the supply chain and reduce development times, thereby reducing costs and improving product quality. Of course, standardization does not mean everyone in the industry uses the same pieces of equipment, with the same designs – flexibility and using the right equipment for the process is important. A lot can already be achieved by using similar practices and standardizing the components used. Systems have a tendency to drift apart over time, and it's important not to let entropy take over – new single-use systems or stock keeping units (SKU) shouldn't be put in place unless there is a clear need to do so. A central benefit of this approach is that it makes validation much easier. If the components have been used before within a company or a manufacturing site, the validation documentation should already exist or can at least be adapted – much easier than starting from scratch. Using the same SKUs for multiple applications can also reduce inventory size, which in turn can reduce the warehouse space required – a big bonus given the space requirements of single-use systems. All of this can lead to reduced costs and lead times.

"Standardization does not mean everyone in the industry uses the same pieces of equipment."

No man(ufacturer) is an island

The sector will not reach its potential if

standardization is left to end-users – they must work together with suppliers. The Bio-Process System Alliance (BPSA) has led the way in getting competing suppliers to collaborate, along with end-users. Ideas are exchanged through white papers, which can be taken further and developed into agreed-upon standards. On the website (http://bpsalliance.org), you can find white papers on quality matrices that record how components could be characterized or validated. Pall Biotech has contributed to BPSA white papers on particulates and assurance of integrity – an area of importance when it comes to applying single-use technology to cell and gene therapies as well as more traditional monoclonal antibody manufacturing processes.

The BioPhorum Operations Group (BPOG) has also been instrumental in promoting standardization in single-use technologies. BPOG was originally an end-user organization but, around three years ago, suppliers were invited to participate and they also collaborate with other organizations such as the BPSA. BPOG focuses heavily on what can be described as the business aspects, such as supply chain and change control management as well as technical matters. They have been vocal about their recommended approach to extractables and leachables testing, prompting suppliers to keep to a common standard so that when end-users are conducting risk assessments, they can use the same principles. And this raises an important point: standardization isn't just about components and everyone using the same system. Rather, it's about common business and technological practices that can help streamline the work that everyone does in the field.

Such streamlining also applies to training. Single-use systems involve a lot of manual interventions, which can lead to operator mistakes, if individuals aren't well trained. Single-use stirred tanks, for example, are heavy and require significant handling, while also containing several complex tubing assemblies and inlets/outlets. In fact, one company found through root cause analysis that single-use bag failures were caused by three factors: handling (46 percent), supplier defects (28 percent) and operator errors (26 percent). They recommended a combination of system design improvements and training to reduce failures.

Successful training material should be easy to learn, easy to understand, easy to recall and easy to apply. If operators are forced to use different single-use systems that work in different ways, then they will need to be trained to use each of the various systems, making the whole process more difficult to learn, recall and apply. Standardization can reduce this problem and make training less cumbersome. It also facilitates video-based training, where guidance must directly relate to what is in the operator's hands.

The benefits of standardization extend well beyond single-use components and system design. And we need to work together to collectively reap the benefits.

Information Overload

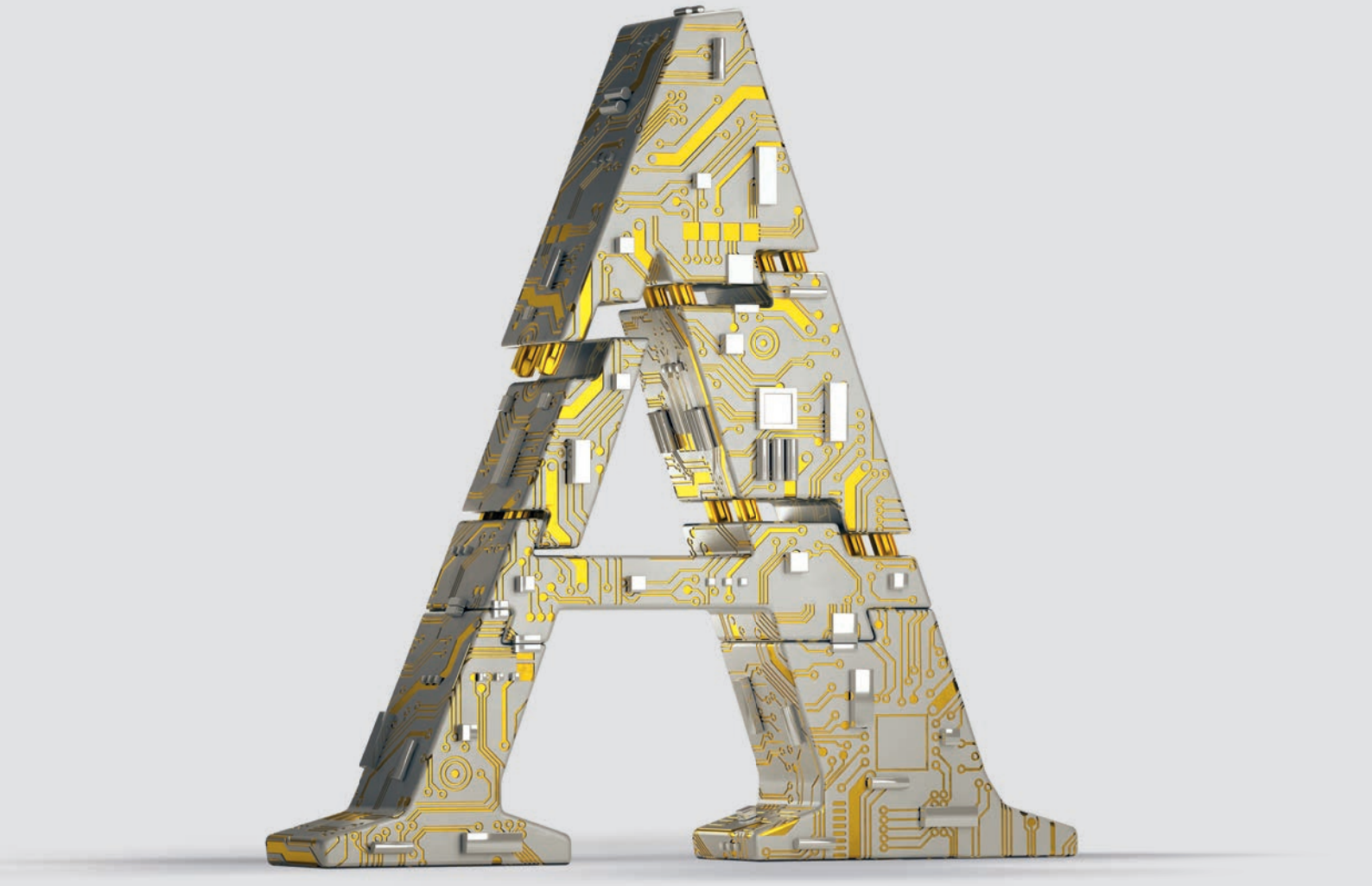
Pall Biotech has developed a proprietary web-based system to organize information pertaining to the ever-increasing number of single-use systems and components on the market.

One major problem for end-users and suppliers is that it can be very difficult to keep track of which combinations of components have already been validated. Pall Biotech found that there was no advanced information management system available that could store all the data related to the increasing number of single-use components on the marketplace. In the early days of single use, this wasn't a problem, as there were only a limited number of single-use systems, with few components – we just used Excel spreadsheets! But as the number of systems and components grew rapidly, we realized that we needed a better approach. We, therefore, set out to create our own solution: the Allegro™ Central Management System (ACMS).

ACMS categorizes components into preferred, nonpreferred and restricted. Preferred components have been extensively evaluated. Nonpreferred components are the next step down: these satisfy regulatory requirements but are not as well validated as preferred components. Restricted components are typically specialized, custom, components. Customers can therefore reduce validation and lead times by choosing preferred components for their single-use system design. The system allows for instantaneous compliance reports and has a built-in configurator that can select components operating within a chosen processing window. It also stores all the designs made for any end-user, which allows the ACMS's advanced search function to find all existing systems which could satisfy additional applications.

The system also stores customer URS documents, including the desired system, project specifications, operating conditions and other project details. We can then use that information to determine whether the enquiry can go ahead. Once approved, the information is used to ensure all materials and designs are fit for purpose, providing traceability for all involved.

We began implementing the ACMS around seven years ago and it is continually evolving as the marketplace develops.



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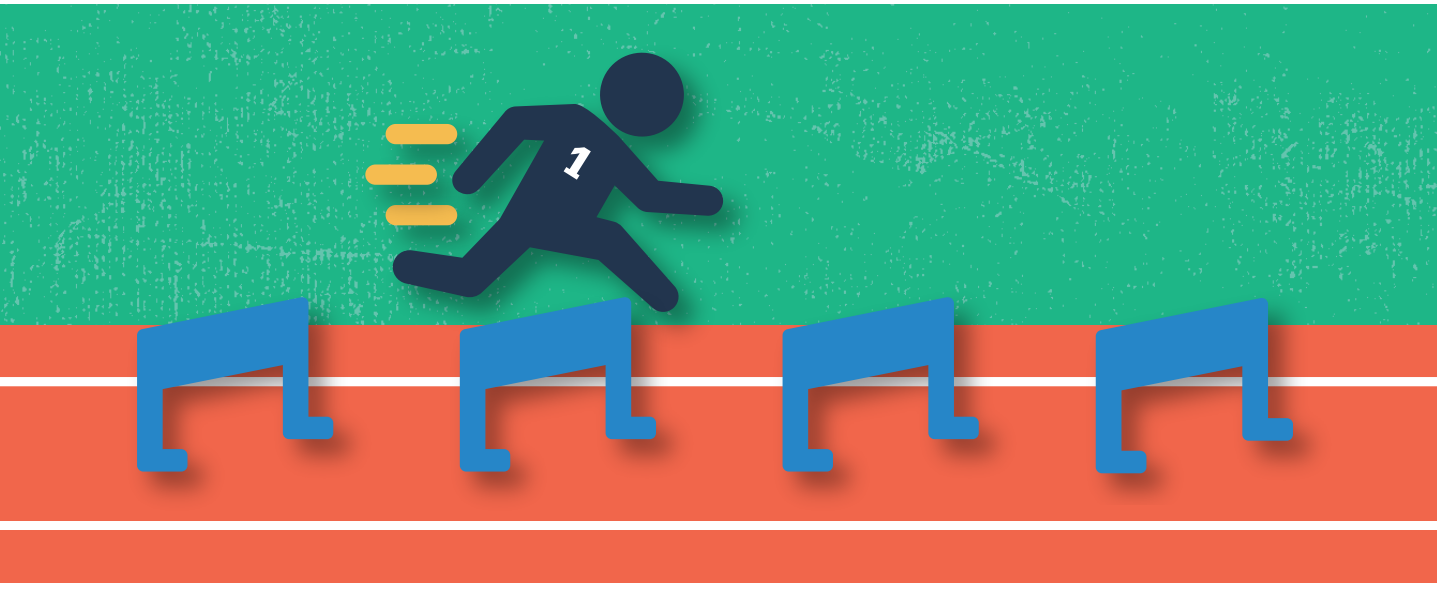


Formulation Fail

Delays arising from formulation issues are commonplace in the industry. It's time to start thinking about the problem earlier.

By Stephanie Sutton

Drug developers have many options when it comes to formulating their products and deciding on the final form that will suit the molecule – and the patient – best. All too often, however, companies leave formulation decisions until the last minute or opt for the "easy" (and cheapest) formulation choice. But if this doesn't work it can result in costly – and sometimes lengthy – delays. And sometimes the easiest option isn't the most convenient for patients.

In 2017, an alliance was born between contract manufacturer Rentschler Biopharma and biotechnology company LEUKOCARE. One of the goals of the alliance was to raise awareness of the importance of considering formulation in the early stages of the drug development process (particularly for biologics). Last year, the companies partnered with Informa Pharma Intelligence to conduct a survey to dive deeper into the topic of formulation (1). Here, I speak with Michael Scholl of Leukocare to learn more about the results.

What inspired this survey?

We wanted to learn from the industry about the current needs and priorities today around formulation. At the same time, we strived to highlight the fact that formulation development of biologics is currently mostly underestimated and unexploited. We wanted to draw the industry´s attention to the topic of (early-stage) formulation and point out its beneficial effect on product commercialization.

What were the most surprising findings?

One of the most surprising findings for me was the fact that 60 percent of the respondents have experienced formulation issues during clinical development, some of which led to significant delays or even complete project failure. This makes formulation a key success factor in the process of drug development. Surprisingly, however, at the same time almost 60 percent of respondents believe that deploying a fully developed formulation should only take place at later stages of clinical development (around phase IIa or IIb). These two answers shed light on two important aspects and confirm our hypothesis when initially setting-up the Strategic Alliance: drug product formulation is a key aspect and value driver in the drug development process, but the importance of considering formulation at early stages is still underestimated by the industry.

"We wanted to learn from the industry about the current needs and priorities today around formulation."

60% have experienced a project failure or significant delay because of formulation challenges

Delays of less than 12 months **38%**

More than 12 months **52%**

Project/product candidate terminated due to formulation challenges **10%**

TOP FORMULATION CHALLENGES:

- Stability Bioavailability (PK/PD)
- Cost
- Drug product safety
- Low solubility
- Shelf life
- Patent protection

MOST IMPORTANT DECISION CRITERIA IN FORMULATION:

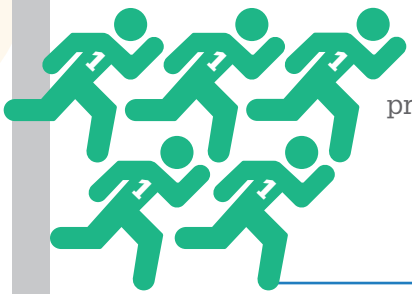
1. Competitive advantage
2. Reduced probability of failure
3. Reduced time to market

WHEN SHOULD A COMMERCIALLY VIABLE FORMULATION BE DEPLOYED?

Most companies **(49%)** say during Phase IIa or IIb but the earlier you start the better!

Only around **21%** of companies invest **$500,000** or more in formulation

In the next 5 years, **39%** of companies expect to invest **$500,000** or more



Formulation, manufacturing, drug product, drug substance and clinical teams get involved in the formulation decision making process.

General management, business development, and marketing and sales are often left out.

"Real competitiveness versus other drug products to increase market share can be achieved by formulations that allow a switchover from intravenous to subcutaneous injection."

57 percent of respondents rated the competitive advantage of formulation as very important. How can formulation give a competitive edge?

First and most often, the initial goal is to obtain appropriate stability with decent shelf-life – prolonging shelf-life beyond two or three years can be an advantage, especially in terms of storage and supply chain costs. Beyond this standard requirement, real competitiveness versus other drug products to increase market share can be achieved by formulations that allow a switchover from intravenous (IV) to subcutaneous (SC) injection, or storage at room temperature. Both features can really improve a patient's convenience and quality of life. This is also an important parameter for drug pricing itself. Think of a patient with a chronic disease who needs weekly or biweekly SC injections, where one product needs to be kept at 5°C at all times, while a competitor allows storage for up to 14 days at room temperature. On first sight, the difference may seem small, but the consequences are significant with the latter product enabling almost complete freedom for business travel or holiday trips without carrying a cooler bag, significantly facilitating a "normal life" for patients suffering from a chronic disease.

Very few companies seem to invest a significant amount of money in early stage formulation projects annually…

We absolutely think that this should be a key focus in the early stages of development. There is a close correlation of an optimal formulation in the context of the target product profile (TPP). Since the TPP is the key developmental and commercial planning tool for therapeutic product candidates, it should include formulation aspects early on to address the value aspects of formulation, as well as strategies to achieve the TPP for maximal competitiveness. We would strongly encourage developmental companies to at least include a proper discussion on formulation work early on in the development process.

In your experience, what are the most common types of formulation challenges that companies encounter?

Classical challenges are the well-known hotspots of biologics such as aggregation, deamidation and unfolding caused by relevant stress such as temperature, oxidation or shear stress, among others. It depends on the compound which ones actually occur most and how they are related. It's advisable to begin any development project with an extensive basic characterization by forced degradation studies to learn about the degradation pathways. Based on this knowledge you can develop a tailored formulation.

The pharma industry has been talking about formulation challenges for many years and today there are a number of

very good technologies and approaches available to help drug developers. But are these being used to their full potential?
Actually, we believe that most developers currently do not yet use available technologies full potential. Very often "off the shelf" formulations are being applied as "good enough" without considering neither the biologic hot spots for degradation nor the TPP with the commercial implications in their formulation development. Too often, it comes up later in development or in commercial context that there is value left on the table or, even worse, critical findings that delay or even stop projects from further development or commercialization.

In recent years, what do you think have been the most important advances in terms of formulation techniques or technologies?
A lot of progress has been made regarding analytical methods and their combination to better understand protein degradation and extrapolate the findings of accelerated aging studies to real time storage. Moreover, enhanced excipient quality has helped to improve formulation development. However, identifying the interplay of several excipients in the stabilization of one molecule, as well as understanding key characteristics of the specific molecule and taking these into account during formulation development, are still – in my belief – not addressed adequately with the necessary importance. In many cases, this is accounted for by restrictions on available time and the feasible number of experiments. New technologies, such as artificial intelligence and machine learning, will likely open a new window of opportunities. We are already taking these aspects into consideration during our rational database-driven and algorithm-based formulation development approach, which aims to develop advanced formulations without large high-throughput screening efforts.

Do you think the industry truly appreciates the importance of formulation or is it just seen as a tool for intellectual property?
I think that there are many layers to this. First, formulation developers surely see the importance of their work, but often have to accept very short timelines, limited resources and limited input from marketing for an optimal formulation that addresses relevant TPP aspects. This is opposing a proper formulation development which, for example, includes added value by formulation IP, among others. Prolonged patent protection itself can be of significant value as each extra month of sales can add massive value to a drug product, especially for blockbuster drugs.

Something that wasn't touched upon a great deal in the survey was the importance of formulation in developing patient-centric medicines that can boost adherence. What are your thoughts on the matter? In your experience, is patient centricity a key part of formulation conversations?
I am convinced that patient centricity in general is a key discussion point for most stakeholders including regulatory authorities, pharma & biotech and physicians. There are already many efforts to enable more convenient applications for patients by improved formulations to allow, for example, subcutaneous self-application of therapeutic antibodies in high concentration or patient-specific dosing. When it comes to adherence, there is a multitude of factors that play a role such as easier administration or storage at room temperature. In principal, formulation can support all of these drug product features.

What top advice and tips would you offer to companies to help reduce delays caused by formulation issues?
It's very simple: "do it right the first time"!

"Classical challenges are the well-known hotspots of biologics such as aggregation, deamidation and unfolding caused by relevant stress such as temperature, oxidation or shear stress, among others."

If you can't do it in house then there are contract developers that can consider all the relevant aspects for maximizing drug product value. And make sure everyone is involved. When considering efficient clinical development, commercial success and patient-centric features, you'll need all relevant stakeholders involved during the drug development process; not just CMC and formulation experts, but also clinicians and commercial decision makers.

Considering an optimal formulation that is right from first-in-man through launch can help accelerate time to market and reduce risk of failure. We encourage and advise everyone to think of drug product right from the start.

Reference

1. *Rentschler Biopharma, Leukocare Biotechnology, "Industry Insights 2018 Survey: Formulation in the Drug Development Process" (2018). Available at https://bit.ly/2DjmtUY.*

A Lifetime of Achievement

Sitting Down With... David Schoneker,
Global Regulatory Director, Strategic Relationships
at Colorcon and Vice Chair for Science and Regulatory
at the International Pharmaceutical Excipient Council of the Americas.

What was your first professional job?

In 1977, without having insight into what an excipient was and with only an undergraduate degree in chemistry to my name, I accepted a job offer from Colorcon. I began working for the company just two weeks after graduating. It was an exciting time for me as a young analytical chemist and I enjoyed learning about an area of the industry that had previously been completely unknown to me!

Colorcon was a small company at the time (I was employee #112). Though the company was relatively new, it was beginning to grow significantly in terms of size and recognition as a major supplier to the pharmaceutical industry. During the day, I learnt about excipients at work, and in the evenings, I attended night school at Villanova University to get my master's degree. The opportunities for academic and professional growth really helped me manage and grow into my new role.

How did regulation become an integral part of your career?

My early role was as a green bench chemist checking that our excipients met the company's quality standards. Relatively quickly, I progressed from Manager to Director of Quality Control for North America. The company had no separate regulatory department back then, so I ended up splitting a lot of my time between my own role and providing regulatory support for the company to assist our customers and our own internal R&D groups. It wasn't until 1995 that the company developed the in-house regulatory department, which helped us share our expertise in the field of excipient design, and international regulations across the industry.

You've also been very much involved with IPEC…

Correct! I've been involved with the International Pharmaceutical Excipient Council (IPEC) from its founding in 1991, and I am sincerely proud of the association's accomplishments. Our early goal was to harmonize compendial standards for excipients, as well as GMP guidelines and safety evaluation guidelines. It is incredible how much IPEC has grown over the years. And through my involvement with IPEC, I became more deeply involved in Colorcon's regulatory affairs. It's an area I am very passionate about; it's so important that we continue to improve the regulatory framework surrounding excipients so that excipient manufacturers know what is expected of them, and pharmaceutical companies understand the realities of excipients when formulating drug products.

How did it feel to receive IPEC's Louis Blecher Outstanding Lifetime Achievement Award?

Receiving the award came as a complete surprise to me, as it requires a nomination to be submitted to the Foundation's board detailing the significant contributions an individual has made to IPEC. Though I was blindsided, the award carries sentimental value for me. Lou was a close friend of mine until he passed away in 2008. Having known Lou – and his passion, enthusiasm and drive to change the way an entire industry looked at excipients – made winning the award even more meaningful. He was the one who brought us all together to found IPEC. In those early days, he dubbed me "The Young Scientist" for my penchant for piping up from the back of a meeting with questions and comments. I was often the youngest person in the room but didn't shy away from letting my voice and ideas be heard!

Lou was the first recipient of the IPEC Foundation Chairman's Award, which was created to reward individuals who have made substantial contributions to the field of excipients. The award was renamed in his honor.

How would you like to see the industry progress?

Formulators weren't vocal enough in the past to hold the attention of the industry when talking about the importance of excipients. But over recent years, regulators have thankfully become more aware of how essential the quality of excipients is to the overall quality of drugs produced. Unlike APIs, excipients are not pure. They are made of multiple components, including additives and residual processing aids that are inherent to the way that these products are made, all of which have the potential to have significant effects on their performance. In our experience, pharmaceutical companies will often be tempted to buy from cheaper sources so long as the excipients meet US Pharmacopeia specifications for drug development, disregarding the fact that the compositional differences between excipients can impact the final drug product.

IPEC seeks to help formulators understand that underpinning the variation seen in their finished drug products requires an understanding of the inherent differences caused by using excipients from different suppliers. The materials may meet the same basic specifications, but without doing all the same studies (e.g., stability, compatibility) with each supplier's material during the original drug development, the materials are not interchangeable. IPEC has published a guideline in this area, "The IPEC Excipient Composition Guide 2009" and I have personally delivered seminars to help drive conversation around this issue and change the perception that certain excipients from multiple suppliers are fine to use as substitutes so long as they meet the broad specifications that are currently listed in the pharmacopeias. We hope that this will help users and makers communicate better as it relates to excipient composition profiles and the impact that compositional differences may have on drug manufacturing and performance.

Despite the challenges we face, I can see change happening in the industry and this makes me very optimistic about the future of the field. We still have a long road ahead of us, but I know that so long as we continue to make our voices heard, more progress will be made. In the 30 years that IPEC has existed, it has revolutionized the way excipients are viewed. Here's hoping that the next 30 years will be just as successful!

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