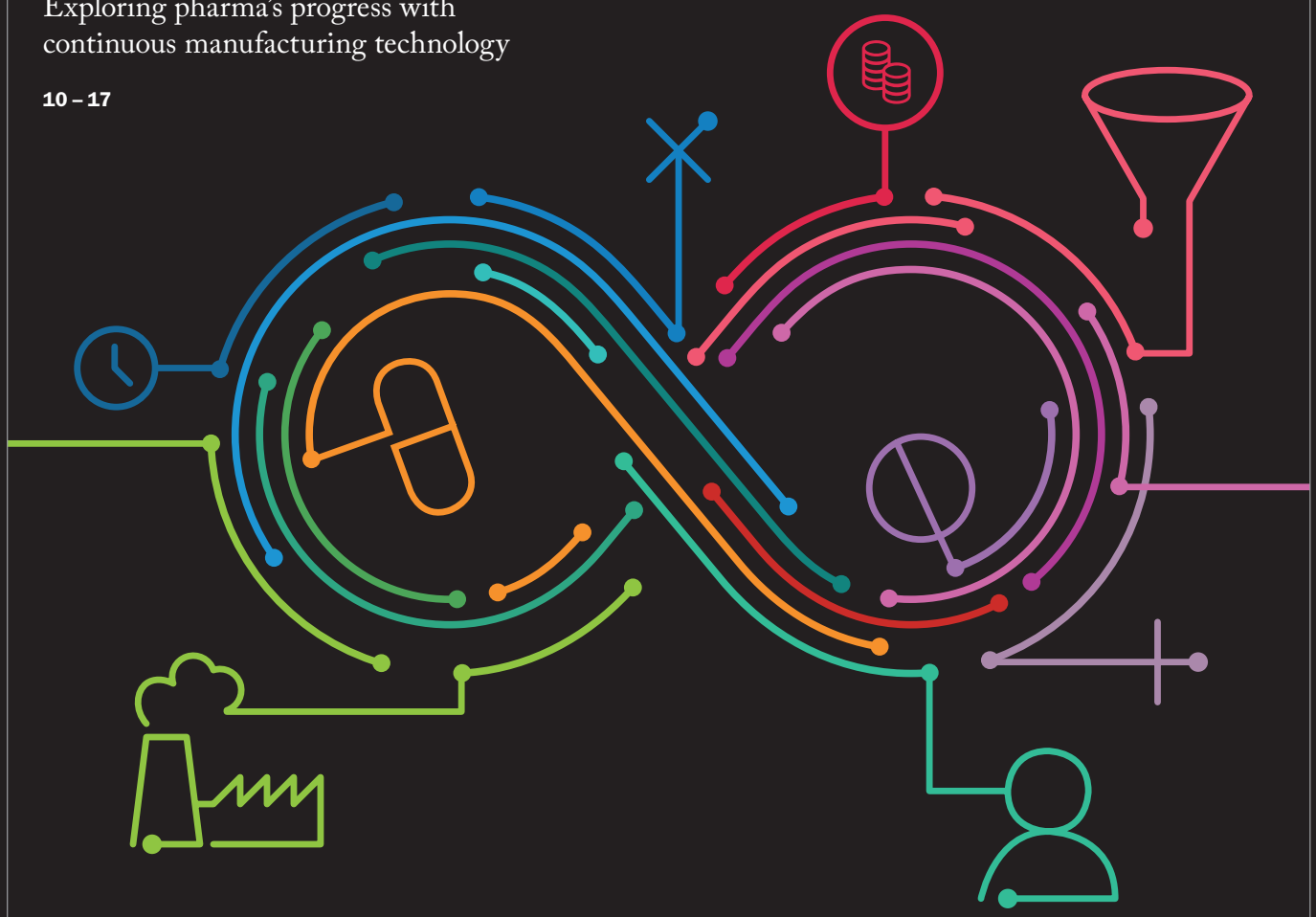
NOVEMBER 2019 # 02

the Small Molecule Manufacturer™

In the Loop

Exploring pharma's progress with continuous manufacturing technology



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the Small Molecule Manufacturer

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Bang the Drum

Pharma companies have been raising awareness for years, but patients continue to buy counterfeit medicines online

A recent study claims that up to 60 percent of search engine results for the antibiotic Bactrim (trimethoprim/sulfamethoxazole) led to dubious websites and potentially counterfeit medicines (1). Even without the study, people connected to the pharma industry are well aware of the countless websites selling what should be prescription-only medicines. Both small molecule drugs and biologics are affected, but the former typically come in convenient tablet form, making them easier to replicate and more accessible to consumers.

Pharma companies have been raising awareness of the issue for years. As just one example, Sanofi trained around 20,000 people in 2014 as part of its commitment to combat counterfeit medicines. The company also trained 7,300 public agents (2). And though the costs of training were not given, the number of people involved suggest the outlay was significant. At a time when drug pricing is firmly in the spotlight, it is unfortunate that the onus is on pharma companies when it comes to ensuring that patients are aware of the real dangers of counterfeit medicines.

Pharma's commitment to countering counterfeiting is partially self-serving (even illegal competition is competition), but the focus is firmly on safety. Pfizer has a lab dedicated to analyzing counterfeit medicines, which has previously discovered brick dust, boric acid, and even floor polish in tablets. And though track and trace initiatives have been launched to help prevent counterfeits from reaching legitimate pharmacies and hospitals, online counterfeit medicines are more difficult to tackle, with consumer behavior playing a key role. Google has reportedly said that it will not take action in terms of de-indexing URLs dedicated to selling counterfeit products, including medicines (3). And until search engines are willing (or forced) to step up, pharma must continue to beat the drum with awareness campaigns. Young people, for whom online shopping is second nature, are an especially important target group, and so Pfizer is reportedly launching a new campaign in the UK – "Don't be catfished by counterfeit medicines" – to target students.

What else can – or should – pharma companies be doing? And which other stakeholders could help foot the bill when it comes to awareness campaigns that benefit public safety? I'd be interested in hearing your thoughts on the subject (stephanie.sutton@texerepublishing.com).

Stephanie Sutton
Editor

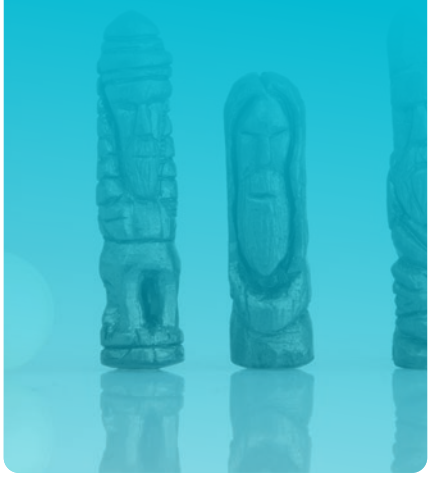
References

1. *European Pharmaceutical Review, "Sixty percent of search engine results for medicines yield counterfeit drugs," (2019). Available at: https://bit.ly/2ompYUM. Last accessed October 25, 2019.*
2. *Sanofi, "Fighting Counterfeit Medicines," (2017). Available at: https://bit.ly/2BGtxYL. Last accessed October 25, 2019.*
3. *Incopro, "How and why search engines must take responsibility for tackling counterfeiters," (2019). Available at: https://bit.ly/32NOyfZ. Last accessed October 25, 2019.*

Upfront

Reporting on the trends, personalities and industry announcements that are shaping small molecule manufacturing.

We welcome information on any developments in the field concerning small molecules that caught your eye, in a good or bad way. Email: stephanie.sutton@texerepublishing.com



Art in a Capsule

The search for miniscule masterpieces

Earlier this year, ACG launched the 'Art in a Capsule' competition. Ajay Kumar Mattewada scooped the top prize of $5000 after creating a flag bearer riding a horse – the piece was small enough to fit onto a pinhead. We caught up with Peter Neve, Chief Marketing Officer at ACG, to find out more about the competition – and the winner.

What inspired this competition?

Art and science belong together because they both require imagination, vision and a deep understanding of their respective expertise. Bringing these two fields together, we wanted to find a way to create a unique challenge that would inspire people. As we make over 100 billion capsules per year, this seemed like a great focus for the competition. Thus, the Art in a Capsule competition was born. I am very pleased at the response we have received from across the globe. It's amazing to see what artists have created to fit inside the capsules!

How did you judge the competition?

The judging panel comprised of people from varied backgrounds: Vishwanath Sable is the Dean of one of the premier art institutes in India – JJ School of Art; Nandini Singh is an avid art collector and has worked with artists across the globe; and Nina Neve is an art connoisseur who has worked very closely on international exhibitions. Collectively, they judged the art on three parameters: originality, execution, and "wow" factor.

What made the three winners stand out?

Ajay Mattewada's art entry was titled: 'A flag bearer sitting on a horse on the pinhead.' He executed the idea with such great detailing that it was a clear winner across all three parameters. It really had the wow factor for everyone that saw it!

The second prize winner was Rusi Barucha, with his miniature sculptures on pieces of pencil lead. He mesmerized us all with its detailing.

Arthur Lazaryan, the third prize winner, shared art titled 'Finally got the goldfish' and 'During Nirvana.' The art pieces were so tiny and yet so beautifully detailed that we couldn't help but just admire in awe.

What was the Judge's Discretion category – and who won it?

This category was not planned initially, but there were two art pieces that just stood out for the judges and a special category had to be made for them. The first one, by Silas Gonzalez, was titled 'Asleep' – and featured a sleeping man in a coffin. The artist even sent us the dirt to go with the coffin! This was a concept that stood out and won the hearts of all the judges alike.

The second one was 'Tiny Einstein' by Jessica Noelle Morse. From the expression, to the hair, Einstein's moustache and the stance – everything was so beautifully captured by the artist that we couldn't let it go without winning something.

Will you repeat the competition next year?

Yes! We were so pleased with the response this year that we are planning to repeat the competition on an annual basis. It is a great way to highlight pharmaceutical capsules in a totally new way. We look forward to increasing the publicity and number of entries each year as the competition becomes more and more established.

I really must say a special thanks to all the artists who spent so much time working on miniature artworks for the competition. We really had no idea if the concept would gain sufficient traction, so it was a great relief when the entries started to flood in. To help recognize this success we are printing a book to celebrate all the artists and their entries – each of the artists will be sent a copy of the book as a momento of their contributions. We also plan to set up a permanent exhibition of the entries in our Research and Development offices as a permanent record of the event.

What's Going On?

Facility expansions, deals and controversies from across the small-molecule drug development space

Facilities

- Albemarle Fine Chemistry Services is expanding operations at its Tyrone, Pennsylvania, custom manufacturing facility. The new 8900 square foot facility includes a control room and data center and a 2000 square foot quality control laboratory. Relocating the quality control operations to the newly constructed building will also free up an additional 1500 square feet of space to allow for expansion of the existing R&D laboratory.
- Unable to find a buyer for its small molecule manufacturing site in Clarecastle, Ireland, Roche is looking to exit the site by March 2020. The move is part of Roche's strategy to downsize its small molecule manufacturing capacity, which was announced in 2015.
- PCI Pharma has expanded its Clinical Services facility in Rockford, IL, USA, by 30,000 square feet, featuring increased flexibility and scalability for primary and secondary packaging, labeling, and 2-8°C cold chain storage.

Deals

- ACG Engineering, part of the ACG Group, has acquired Xertecs GmbH, a pharmaceutical processing equipment company. Xetecs' portfolio includes conceptualization; design engineering; prototype development; automation design and integration into MES systems; development and optimization of components; complete plant design including 3D modeling; process optimization and delivery of new process equipment.
- Civica Rx and Exela Pharma Sciences have announced a long-term agreement to manufacture and supply Civica's growing membership of US health systems with sodium bicarbonate injection, which has been in critically short supply in the country's hospitals. Exela will produce the sodium bicarbonate using the company's Abbreviated New Drug Application and Civica's labeling and National Drug Code (NDC). First deliveries to hospitals are expected this year.

Controversy

- The UK's National Health Service has received a payout of £8 million from an unnamed pharmaceutical firm, after the firm was found to be using anti-competitive practices that increased the price of fludrocortisone – a life-saving small molecule drug for patients with Addison's disease. Two other pharma companies are also being investigated for their involvement.

Role Call

Small molecule drug development and manufacture involves countless people in many job functions. Each issue, we highlight a different industry expert; here, we speak with Matthew Moorcroft, Vice President of Marketing & Intelligence at Cambrex

What does your role involve?

In short, my role is about supporting the Cambrex businesses with a marketing communications team that is smart, driven and effective, as well as working with the company presidents, executive management team and Board of Directors to provide market intelligence that is accurate, reliable and timely.

Two years ago, I relocated to the Cambrex head office in NJ, USA to support with corporate development and mergers and acquisitions, and have since supported the recent acquisitions of Halo Pharma and Avista Pharma Solutions. Though all of these activities take the majority of my time, I think I am still a nerd at heart and spend the rest of my time researching the pharmaceutical market, analyzing data, authoring articles, and sitting (for probably more hours than are good for me) in front of a computer writing PowerPoint presentations.

Why did you join Cambrex – and what do you hope to achieve?

I was excited to have the opportunity to join Cambrex in 2014 because the company had a clear vision to become one of the largest and fastest growing companies in the small molecule space. My role was to help build a marketing and intelligence team that would be responsible for the rebranding and marketing of the company, and to help support the transition towards a data-driven culture for strategic decision making. Today, we are now considered a world-class CDMO through our hard work and dedication to small molecules and chemistry. Our organic growth strategy has culminated in many industry awards, including the Fortune award for the Top 100 Fastest Growing Companies.

Our growth continues and we were excited to announce recently two acquisitions that allow us to access other parts of the outsourcing continuum in drug product and analytical services – Halo Pharma and Avista Pharma Solutions. These acquisitions provide Cambrex with the opportunity to access new markets.

Some say that the days of small molecules are over…

I would listen, smile and gently remind them that the world is still small… molecules! There is no denying the growth of competing modalities, such as monoclonal antibodies or gene therapies, and the continuing development of new technologies. Prior to Cambrex, I worked for Lonza and had the opportunity to work with many talented people across many molecule types, including monoclonal antibodies, recombinant proteins, cell and viral therapies. I was also lucky to be part of the team that worked on the world's first biosimilar, so it is fair to say I have been on both sides of the fence. In the same vein, there is also no denying the fact that the overwhelming majority of patients are still treated with small molecule drugs – an industry that started in the mid-19th century and continues to flourish. Drug approval rates for small molecules have been trending upwards and are currently at a 20-year high, and we also see more molecules in the clinical pipeline than ever before. To put this into perspective, when I look back there are around 40 percent more small molecule NCEs in clinical trials than when I started my job at Cambrex five years ago. Given those numbers, I don't know how much bigger you can get.

Sources: ReportLinker, "Pharmaceutical Excipients Global Market Forecast to 2025" (2019); FiorMarkets, "Pharmaceutical Excipients Market by Type (Organic Chemicals, inorganic Chemicals, Others), Functionality, Formulation, Regions, Global Industry Analysis, Market Size, Share, Growth, Trends, and Forecast 2018 to 2025" (2019).

A Forecast for Excipients

A snapshot of the global market forecast for the pharmaceutical excipients market

What's the Forecast?

The global pharmaceutical excipients market is expected to reach over

$9.5 BILLION BY 2025

The organic chemicals segment of the market had the highest revenue in 2018 – thanks to their use in most pharma formulations

Sunny Skies for Europe and Beyond

The largest market for pharma excipients is Europe, which had a

41.53% MARKET REVENUE SHARE IN 2017

However, the Asia Pacific region is forecast to have the fastest

CAGR (8.09%)

IN THE LEAD UP TO 2025

GROWTH DRIVERS INCLUDE:

- increasing geriatric populations
- advances in functional excipients
- surge in generic drugs sales
- increasing use of biopharmaceuticals

Plant-based excipients are a particularly fast-growing area because they are cost-effective, biocompatible, have low toxicity with better patient tolerance, and are easily available

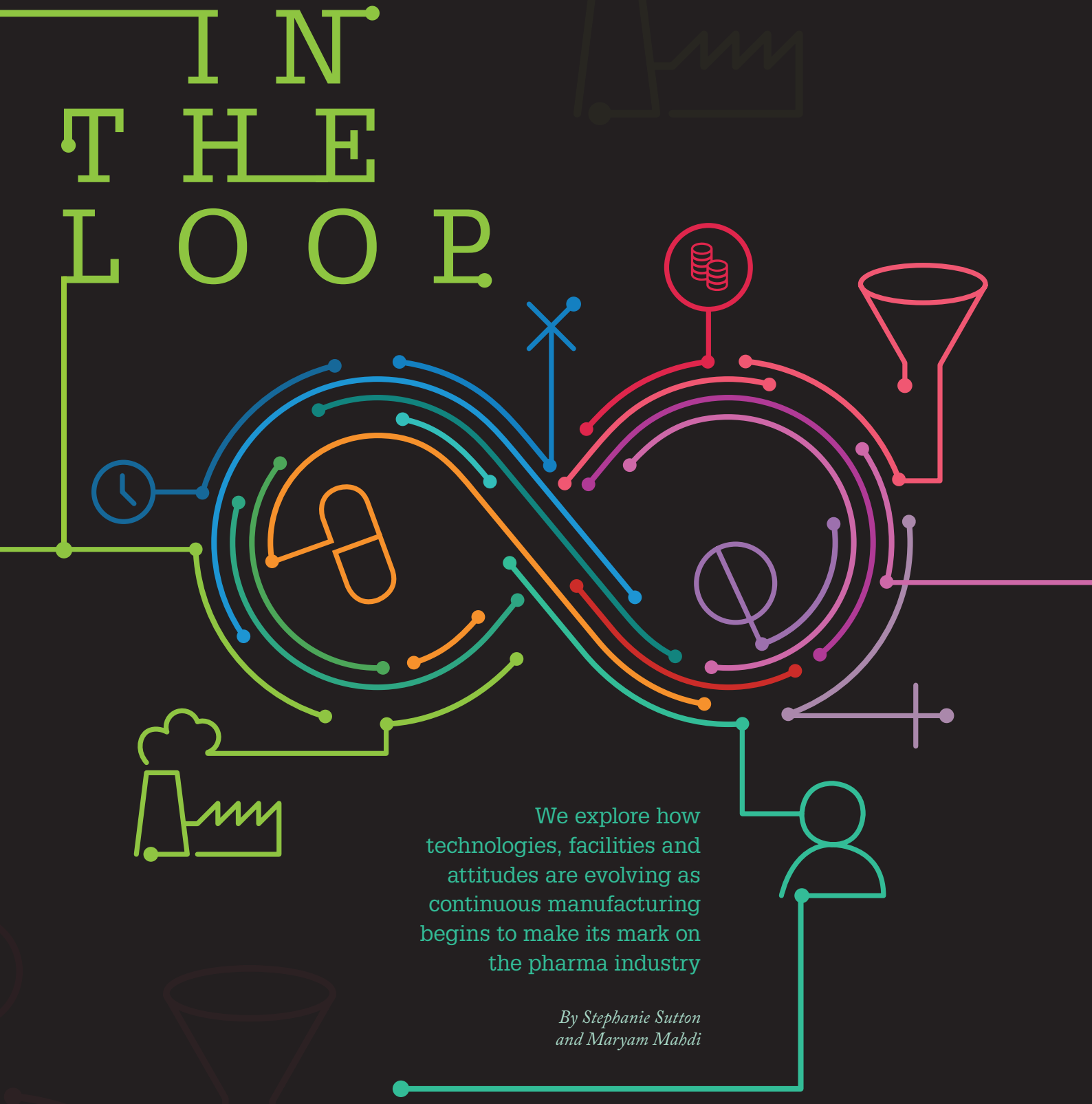
Why Excipients Matter

Solubility of APIs with poor bioavailability is a major problem – excipients can protect, support or enhance drug stability and bioavailability

Excipients also help transport the API to the correct site in the body and can aid the manufacturing process

Overall, stringent regulatory approval processes and the expensive and time-consuming nature of drug development could hold back market growth

IN THE LOOP



We explore how technologies, facilities and attitudes are evolving as continuous manufacturing begins to make its mark on the pharma industry

By Stephanie Sutton and Maryam Mahdi

CONTINUOUS IN THE SPOTLIGHT

Continuus Pharmaceuticals, a spin out from the Novartis-MIT Center for Continuous Manufacturing, describes itself as one of the few companies working specifically on continuous manufacturing; for drugmakers, continuous manufacturing efforts are secondary to R&D, but Continuus was established with the primary objective of shining a spotlight on continuous manufacturing. Bayan Takizawa, Chief Business Officer at Continuus Pharmaceuticals, tells us more.

What's the story behind Continuus Pharmaceuticals?

In 2007, Novartis and MIT embarked on a collaboration, targeting the continuous manufacture of small molecule drugs because they recognized how outdated batch processes were. They wanted to break away from conventional manufacturing and establish the best possible production system for these drugs. The end result was the Novartis-MIT Center for Continuous Manufacturing, which was a huge success. By 2011, they had constructed a pilot line at MIT that integrated both upstream and downstream components into a single continuous process. The team was able to take a 200-day batch process and cut it down to just two days, with the additional benefits of reduced footprint (approximately 90 percent reduction), reduced costs (30 to 50 percent), reduced environmental impact, and improved quality.

Continuus Pharmaceuticals is a spin out from the Novartis-MIT collaboration – and many of our team members and advisors were critical architects of the original project, including Bernhardt Trout (Professor of Chemical Engineering at MIT) and Tom Van Laar (former head of Global Tech Operations, Novartis). We have also now brought in other outside thought leaders as well. The goal? To bring the benefits of integrated continuous manufacturing to the broader pharma industry and transform small molecule manufacturing.

What is integrated continuous manufacturing?

There are many different definitions of "continuous manufacturing" across the industry, with companies taking different approaches. Many are implementing batch technologies or batch technical unit operations in a semi-continuous or continuous fashion, but the overall paradigm is still batch. Other companies have integrated flow systems for part of the manufacturing process; for example, Vertex Pharmaceuticals has a drug product continuous process, but they have not integrated the upstream API components.

We are leveraging an integrated continuous manufacturing system that spans the entire production process. Instead of fragmenting the system into separate API processing and drug product processing operations, we have combined everything into one seamless line. There are many benefits with this strategy. For instance, in current/traditional manufacturing systems, many drug product manufacturers have to include corrective steps because of undesirable physicochemical properties introduced by their upstream counterparts. This lack of coordination can make processes very long, expensive, and worst of all, prone to quality problems. It is not unusual for it to take 200-300 days to produce a drug (and in some cases well over a year!), and many of the steps are manual and prone to human error. A more automated and seamless process can remove these mistakes and improve product quality. Integrated manufacturing breaks down siloes and considers the entire manufacturing system, rather than just part of it.

How is it possible to go from a process taking 200 days to just two days?

There are many factors that contribute to the reduction. First is the decrease in the number of steps required by eliminating corrective ones, as we consider the process as a whole rather than just the API or formulation. Many steps are also much faster; for example, the residence time for our continuous filter and dryer is in the order of a minute, whereas it can be many hours for a corresponding batch process. Of course, all of this does not get you from 200 days to two days! The biggest contributor is removing the starts and stops that batch manufacturing requires after each unit operation for quality tests to be performed. With ICM, quality is ascertained in-line, using real-time monitors and process analytical technologies that enable the quality of the process material, and ultimately the final drug product, to be predicted. In the current paradigm, when you produce the API, it must be tested and released, creating a long lag time between API production and subsequent formulation steps. With integrated continuous manufacturing, the API remains in situ, and just moves onto the next step. When you avoid those stops and starts, you start to observe a significant reduction in manufacturing time.

What advances in the field have caught your eye?

A number of products have been approved with continuous manufacturing components – many are the result of collaborations similar to the Novartis-MIT. Vertex, for example, is working with GEA, while Johnson & Johnson has been working with Rutgers University, the University of Puerto Rico, and other partners through the Center for Structured Organic Particulate Systems (C-SOPS). Johnson & Johnson actually received approval to produce one of its products, originally approved for batch manufacturing, with a new continuous process.

We have engaged multiple companies with our integrated continuous manufacturing platform, with projects ranging from targeted solutions, where we investigate how a single

unit operation or two can help surmount a specific technical challenge, to broader-scope projects, featuring end-to-end solutions. We have also been working to advance the technology by improving and modifying unit operations. For example, we have developed a more robust and commercial-ready control system with a partner company.

Much of the interest and concern in the field is related to how regulatory agencies will react, particularly the FDA. We believe they have been pretty vocal about their support for the adoption of better manufacturing systems – not necessarily for the economic benefits, but mainly because of the potential for improved quality and patient safety. To that end, the FDA has engaged with the industry and academia to better understand continuous manufacturing. In fact, we are finishing a three-year project with the Agency, where we are examining and demonstrating how quality can be improved through integrated continuous manufacturing.

For pharma companies, quality is essential, but costs are also important. There are enormous pressures right now to bring down drug prices – we see it in the news all the time. As a result, many companies – who previously said they were not interested in continuous manufacturing – are coming to us because they know they need to be more efficient and cost effective in their manufacturing activities.

There is a growing realization that manufacturing systems cannot stay the same forever.

EYES ON EQUIPMENT

What innovations are enabling a changeover to continuous?
By Richard Steiner

I'll begin by saying that the term "continuous" is, in many cases, incorrectly used – particularly when referring to "truly continuous" or "discrete continuous" solutions. Continuous processing goes beyond putting well-defined unit operations together in a line; it is about transforming indeterminate quantities of raw materials into a final dosage form by controlling the process with an understanding that any deviation of a critical process parameter (CPP) is directly linked to the product's critical quality attributes (CQAs). A smart process maintains those CQAs within their tolerance limits without risking material loss or end-product quality. Some prominent unit operations already operate in a continuous manner, such as twin-screw extruders or linear powder blenders. Anyone who claims to be able to accurately define the indefinite quantity of a continuous material stream for their own benefits will come to realize that greater engineering minds will relish the reductio ad absurdum argument opportunity… and win!

Continuous manufacturing in pharma is gaining momentum because of the growing realization that it is a very efficient way of making drugs, moving away from stepwise and time-consuming batch methods to a fully integrated and closely controlled process that gives excellent product consistency by intrinsic design. Regulatory agencies, such as the US FDA, are also advocating the implementation of continuous manufacturing. The FDA states: "If drug makers paid more attention to high quality manufacturing, it would prevent the regulatory problems that lead to plant closures and costly fixes. Continuous processing also allows manufacturers to respond much quicker to changes in demand, potentially contributing to the prevention of drug shortages." (1)

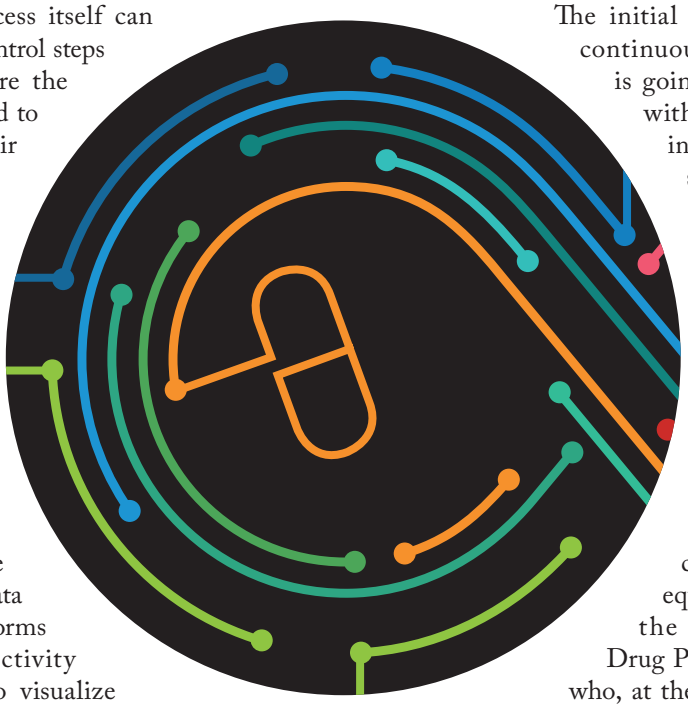
As one example, consider Pfizer's portable, continuous, miniature and modular (PCMM) pod-based mini factories. The PCMM system accelerates the speed at which tablets are produced and by miniaturizing the equipment, the continuous process can be enclosed in a portable, modular facility, which can be shipped by truck to any location in the world and quickly assembled. Once up and running, the system will deliver the capability to transform powders into tablets in minutes, which can take days or weeks with current technology.

The argument that continuous manufacturing is best suited for "large-volume, low-cost" medicines is somewhat dated. In fact, we're seeing the exact opposite. If you look at market approvals and new launches, it's quite clear that drug manufacturers are testing and challenging the business case for continuous manufacturing with legacy products, and then using the same platforms to develop higher value pipeline products and file for new drug applications.

As long as you have pharmaceutical excipients (or an API) in a formulation that can be dosed with a loss-in-weight feeder, you can use a continuous manufacturing system. Often, the decision whether to use continuous manufacturing or not is based more on the "processability" of the powders rather than throughput considerations. The implementation drivers, however, will differ depending on the product. For small-volume products, time-to-market and production yield are key because of the value of the APIs. For bigger volume drugs, supply chain agility and cost savings are the main drivers for continuous.

Equipment innovation

Process intensification in pharma has led to the development of smaller and more compact equipment, but these advances amount to very little without a perfectly designed interface. To cite an example, a critical decision – whether to implement a horizontal or vertical system layout – depends on whether your line must follow the building and material flow requirements of the installation site, or whether you can build from scratch. A brand-new greenfield construction site can readily accommodate a horizontal continuous manufacturing set-up, which, being on one floor, is easier to operate than a vertical one and offers improved efficiency and faster changeover and shorter cleaning times. Often, the interfaces between unit operations (or modules) – whether mechanical, material (physical properties), process (the process itself can become an interface) or the control steps between unit operations – are the biggest issues. Companies need to handle the challenge with their own engineering skills, but should also fully engage with a technology provider that has the relevant knowledge and experience.



The right control system is also crucial; companies must describe the function and control strategy of their system to regulatory agencies, so having the right interface is essential. Today's control systems are highly advanced in terms of data exchange with external platforms (such as open database connectivity clients) or providing tools to visualize process parameters in an operator friendly and interactive way. Data management and PAT tools, such as SIPAT from Siemens, enable much greater levels of process understanding and optimization.

Likewise, we're seeing more and more reliable (and smart) APC systems hitting the market, such as PharmaMV from Perceptive Engineering, which provide higher levels of monitoring, automation and production – for both today and the future – in anticipation of the forthcoming Industry 4.0 initiative. With better control systems come more efficient data use (detail and transparency) and improved productivity. What's most important, however, is the end product: a safe and perfect tablet at the end of whatever process is used. Highly integrated, single-floor production lines equipped with advanced process controls will be the new standard in the future of Industry 4.0 – and continuous manufacturing will be the enabler.

"THE RIGHT CONTROL SYSTEM IS ALSO CRUCIAL; COMPANIES MUST DESCRIBE THE FUNCTION AND CONTROL STRATEGY OF THEIR SYSTEM TO REGULATORY AGENCIES, SO HAVING THE RIGHT INTERFACE IS ESSENTIAL."

The initial financial investment in any continuous manufacturing solution is going to be a challenge; and, as with the implementation of any innovative technology, the early stages are also time-, effort- and cost-intensive, including the associated organizational changes. When – and only when – we establish economies of scale will the financial burden decline as equipment becomes a commodity, as opposed to a tailor-made and engineered-for-purpose solution.

If you are looking to purchase continuous manufacturing equipment, I recommend taking the advice of Fanny Stauffer, Drug Product Lead at UCB Pharma, who, at the 2019 Reality of Continuous Pharmaceutical Manufacturing conference in Durham, UK, said: "Talk – and listen – to your equipment supplier. No one knows more about the technology than the companies who designed and built it. Their insight, guidance and expertise are invaluable."

Richard Steiner is Business Development Manager, Continuous OSD Processing at GEA Group.

Reference

1. *Manufacturing Chemist, "Continuous manufacturing: the facts and the future," (2019). Available at https://bit.ly/2MUQXAi. Last accessed October 28, 2019.*

TO BE CONTINUED...

Hovione's New Jersey–based site has provided process development and small volume API manufacturing since 2002. In the years since its inception, the site has expanded its portfolio to include particle engineering capabilities and the handling of highly potent compounds. And in 2017, the company introduced continuous drug product manufacturing to its roster. Here, we speak with experts at Hovione, including Alexandra Adao (Head of Quality Assurance Continuous Manufacturing), Jose Santos (Head of Drug Product Continuous Manufacturing), Nuno Matos (Head of Quality Systems Management), and Sarang Oka (Process Development Engineer), about the promises and pitfalls of continuous manufacturing and how the facility is faring since it became operational.

Why is continuous manufacturing such an important strategy for drug manufacturers?

For years, the industry has struggled to shorten drug development cycles but many have found themselves limited by the capabilities of batch operations. Requiring less space and resources, continuous manufacturing offers companies the opportunity to manufacture drugs in one facility with a single rig. A major advantage of continuous is that rigs can run for longer when larger batches are needed without the need for scale-up. This could lead to potential savings in API over the course of the entire development cycle (although the API requirement in the early stages of development may be higher). The ability to run development in the same site also means that there is no need to transfer analytical methods and it cuts out the back and forth that often comes when such services are outsourced to other companies.

Big pharma companies are leading the way in proving that the equipment required for continuous operations can also help in lowering footprint. Pfizer's PCMM platform and GEA's CDC50 are also strong examples of the portability of continuous manufacturing equipment and its ability to be used in train with minimum modifications to manufacture using dry compression, dry granulation or wet granulation. PCMM and CDC50 have also been used to alternate between tableting and capsule filling.

Is continuous an inevitability for pharma?

The future of manufacturing in the pharmaceutical industry will need to be continuous, given the push for much more aggressive time to market, enhanced process understanding, and the need to have a higher level of scrutiny of the process – and its impact on the API and resulting product quality. Batch manufacturing can no longer remain the status quo.

The fact that regulators are also becoming subject matter experts by investing in equipment, software for process modeling, and partnering with the leading innovators in the field is also a clear indicator of where the industry is heading.

Why was it important for Hovione to expand into continuous manufacturing?

We installed a continuous manufacturing rig for drug product in 2017 because we believe in the enormous potential this technology brings to the patient. Continuous is giving the company the chance to explore new avenues that weren't possible within the framework of batch manufacturing operations. For instance, we now have the opportunity to open new routes for the manufacturing of pharmaceuticals that weren't feasible within the context of batch manufacturing; to eliminate or reduce the need for scale-up, providing a smoother pathway from development to market launch; and to enhance product quality on the basis of improved process understanding.

In a single shift of our rig, which can be prepared to operate in one of three model (dry granulation, wet granulation, and direct compression), we can process more than 100 kg of coated tablets. The process is heavily supported by PAT, which forms the basis of a control strategy with the potential to segregate material throughout the rig, and ultimately enable real-time release.

What are the most significant lessons learned since the site became operational?

One of the initial challenges we ran into was trying to put together a team with the right skillset. Unlike the teams created to deal with our batch manufacturing operations, our new team dedicated to continuous manufacturing needed a strong background in process modeling, automation, control, and PAT. Our existing teams not only had to adjust to a new way of working, but also to new colleagues whose range of expertise differed from their own.

Moreover, because of the steep learning curve, development is expected to be more challenging when compared with batch operations, with development phases taking more time. But the potential of continuous to be much faster than batch in the full cycle of drug development is obvious, as development is always conducted in the same equipment and at the same scale. Though our experience is still limited, our overall equipment effectiveness (OEE) scores for continuous have already surpassed those for our typical batch processes.

Another key challenge for us as a CMO was efficiency. How would changeover from one product to another affect our capabilities? Changeover is known to have a direct impact on OEE, the relative amount of useful time in the rig. Rigs consist of hundreds, if not thousands, of parts, so changing over is a complex process.

A strategy that we are planning to adopt is to minimize the number of equipment change overs. An example of this is to bundle batches together in longer campaigns with reduced cleaning between batches. We also have ongoing initiatives (including the creation of functionalized work instructions and SOPs, and the use of advanced scheduling methods) to help us address our existing constraints in terms of people and physical space for both cleaning and assembly.

What technological innovations would help increase uptake of continuous manufacturing?

The best route for process development is still unclear, since running a full-scale continuous manufacturing process is API intensive. There is still a debate as to whether a scaled-down development rig is the right approach (some equipment manufacturers are making steps in that direction), or if there should be increased investment in robust methods to identify API surrogates, so they can be used in lieu of the API during development.

It is clear, however, that more industrial examples are required to decrease the perceived risk of continuous manufacturing – existing communities of practitioners are currently working towards such a goal by working together to populate databases of process performance and materials.

The Devil's in the Details

By Marcial Gonzalez, from Purdue University and Center for Particulate Products & Processes (CP3), and Dale Natoli, from Natoli Engineering

The reported benefits of continuous manufacturing for small molecules over batch manufacturing include accelerated product and process development, higher product quality, and reductions in capital, operational expenditures, and footprint. But to achieve higher product quality, the process operation needs to be maintained under a state of control – in general, based on product and process knowledge, and advanced model-based techniques, such as data reconciliation, model predictive control, and risk analysis.

For pharma to move to fully continuous manufacturing, strategic and concurrent adoption of modern process systems engineering tools is needed. In particular, companies must take into consideration the ability of their equipment to connect with automation systems. Systems integration and automation systems, as well as supervisory control and data acquisition tools, are crucial to achieve reliable process operation. Tableting machinery, for example, needs to be complemented by advanced manufacturing components, such as process mechanistic modeling, online, inline and at-line process analytical technology, fault diagnosis, material tracking, and real-time risk assessment. For such process analytical technologies to be implemented, however, companies may have to consider modifying their tablet presses to gain access to the powder inside of the feed frame assembly. Similarly, the tablet press hopper may need to be redesigned to better accommodate upstream and downstream flow variability, and to install content uniformity and mass flow rate sensors.

The measures for quality control of tablets in the context of a continuous process are not necessarily different from those used in the context of batch manufacturing, but continuous manufacturing systems can be equipped with control systems that are handling raw material variability and assuring product quality in real time. For these control systems to be successfully designed and implemented, a robust communication network, a redundant real-time sensor network, mechanistic reduced order models of unit operation, and model-based data reconciliation framework are essential.

After developing and implementing the process systems engineering tools needed for continuous manufacturing and building process knowledge and a data-rich process historian, one can identify optimal and robust manufacturing routes, sensor placement, operation conditions and, naturally, whether batch, end-to-end continuous, or hybrid configurations are preferable.

Similar control systems can be applied to batch operations by implementing real-time process monitoring and then designing a control strategy to enforce quality at the end-point of each unit operation, but the same levels of efficiency and eco-friendliness (along with the other benefits that continuous manufacturing could provide) may not be achieved.

But the adoption of continuous manufacturing will not happen unless the industry's mindset changes. Fortunately, the challenges of developing new generations of equipment, sensors and automation are being embraced by academics, equipment manufacturers, and pharmaceutical companies. Similarly, some regulatory agencies are working with both the industry and academia in an effort to better understand continuous manufacturing.

UPDATING THE TOOLBOX

Batch production has traditionally been – and still is – the mainstay of the pharmaceutical manufacturing sector. However, the economic and technological advantages of continuous flow chemistry are driving adoption by API manufacturers.
By Jonathan Knight and Shawn Conway

Historically, continuous flow chemistry has been reserved primarily for highly energetic and/or hazardous reactions. In batch mode, these reactions have been limited to small vessels and minimal inventories to produce small quantities in facilities that may require bunkers and isolation in a location away from main manufacturing areas. In this way, if an uncontrollable event should occur during a reaction, the risk to personnel and the surrounding area could be minimized and any damage would be contained. Unfortunately, these facilities are expensive to build and maintain, and the small scale of the reactions limits their cost-effectiveness, with their remoteness adding additional logistical complexity, increasing headcount, time, and ultimately cost. For example, Cambrex has a long history of manufacturing and handling energetic compounds and reagents. The inherent explosive nature of these compounds and reagents meant that large scale production needed to be carried out in bunkered production facilities at a site in Karlskoga, Sweden, dating back to when the site was founded by Alfred Nobel in 1896.

In pharma, continuous flow chemistry has traditionally been limited to a specific subset of reactions and synthetic processes, driven by efficiency and cost-savings, with nitrations being among one of the most common processes undertaken. One of the biggest obstacles for companies looking to expand development capabilities in continuous flow, however, has been the lack of suitable commercially available equipment, but in recent years this has changed. Driven by the availability of new technologies and equipment, as well as the need to develop drugs faster, more cost-effectively and for smaller patient populations, there has been a growing movement towards replacing batch production with continuous flow operations. A number of large companies have invested in continuous flow operations for API production, as well as formulation, or both. For example, GSK has invested in continuous flow API development capabilities at its facilities in the UK, US and Singapore; while Vertex, Merck Sharp & Dohme, and Johnson & Johnson have invested in continuous flow formulation technology. Novartis, in collaboration with the MIT, has also spoken of its plans to combine continuous flow synthesis and continuous flow formulation.

Cut costs as well as risk

Safety represents a key advantage of continuous flow chemistry, which minimizes exposure and risk, so that energetic chemistries or hazardous reagents can be handled safely as a feasible process option. But there are also economic benefits of converting energetic and hazardous reactions from batch to continuous flow; it reduces the effective volume of a unit operation and enhances control. By enabling these operations to take place in a regular manufacturing plant, they can be linked more directly to other downstream processes, giving the advantage of operational integration.

Looking more closely at cost, the most striking difference between continuous flow and batch production is the comparative investment for a new plant, with the rebuild of a batch facility costing up to four times more than a comparable continuous flow facility. A smaller equipment footprint, which could be less than half that required by a traditional batch operation, and associated infrastructure can also drive capital expenditure down significantly. Handling smaller reaction volumes also means that energy consumption can be cut by implementing continuous flow synthesis, with solvent usage and associated process intensity also being significantly reduced. Additionally, continuous flow requires less labor and may lead to fewer analytical procedures, representing a significant reduction in operating expenditure.

Efficiencies gained from yield and quality improvements can make a further contribution to reducing operating costs. Optimizing the process can reduce lengthy reaction times and extensive work-ups, drastically lowering occupancy requirements and reducing the plant time required for a given process. Continuous flow chemistry can often replace the use of low temperature (-70°C) chemistry, where it is used to reduce the formation of unwanted by-products. As well as reducing the cost of a project, this can also free up capacity for additional production and revenue.

Aside from the obvious advantages of continuous flow that are realized once a compound reaches commercial phases, it should also be pointed out that the overall development phase can also be shortened considerably. Depending on the required volumes for a process as it moves through the different clinical phases, the same equipment used for early development can move through later phase batches, and potentially even into commercialization. Streamlining the traditional batch-based workflow could even eliminate the scale-up phases of the development cycle entirely, saving not only the cost of those batches, but also reducing time to market by months or even years, enabling development investment costs to be recovered sooner.

Simplifying scale up

Even if scale-up phases cannot be eliminated, continuous flow often allows for easier and more cost-effective scale-up. Scaling up a continuous flow process typically does not require the same magnitude of scale increase and, for some compounds, increased throughput can be achieved by simply running longer, or the addition of another reactor of the same size to run in parallel ("scaling out"),

thereby reducing validation and investment costs significantly.

When discussing scale-up, controlling temperature is critical to success, and this is particularly true when dealing with exotherms within a reaction. In general, the ratio of heat transfer surface area – commonly the jacket surface area – to the overall reactor volume drops by at least an order of magnitude when a process is scaled up from a laboratory or pilot demonstration batch to a modestly sized production run. This drop in the ratio hinders the ability to remove the excess heat from the reaction mixture, possibly putting the material at risk as it reaches a temperature limit. It can also lead to localized hot spots within the mixture, which can cause non-homogeneity and therefore inconsistency. The practical solution is frequently a reduction in the addition rate of a key reagent. However, this can lead to extended times at reaction conditions that can result in degradation, side reactions or even potentially runaway conditions.

In the scale-up of a flow process, the reduction in the surface area to volume ratio is less significant. For example, a 4-inch diameter tube reactor has approximately the same ratio as a typical 0.5 liter laboratory reactor; more typical tube or pipe reactor diameters will have considerably higher values, ensuring that temperature control and exotherm management can be handled in a straightforward manner. For a flow process that uses stirred vessels or continuous stirred tank reactors (CSTRs) instead of tube reactors, the exotherm impact can also be managed by using smaller reactors in parallel, leveraging throughput and providing the necessary production, while also minimizing the scale-up impact. Similarly, continuous flow can overcome the effects on accelerated reaction kinetics of inefficient mixing in large batch reactors, which can extend reaction times and degrade any process time gains.

Furthermore, after a reaction is completed at elevated conditions the process is typically returned to ambient or near-ambient conditions for quenches, work-ups and subsequent process steps. The large thermal mass in a batch reactor takes a considerable amount of time to adjust, which not only further erodes process time gains, but also exposes the reaction mixture to extreme conditions for an extended period of time.

Finally, higher temperatures may have undesired effects on reaction selectivity, while also significantly increasing the risk profile and potential dangers with solvents being raised to, or above, flash points and reaction mixtures purposely being raised to the point where runaway conditions or over-pressure conditions are a real possibility.

Continuous flow offers a scalable solution to these pitfalls. Smaller instantaneous volumes drastically minimize mixing impacts, and concentration or temperature gradients, and also bring the amount of material that is in an elevated risk status to a much more palatable level. The reduced thermal mass makes the process of temperature quenching orders of magnitude quicker, allowing for a rapid introduction to elevated conditions to drive kinetics, followed by a rapid return to ambient conditions for further processing or to protect the integrity of the products or intermediates that are being formed.

Breaking with tradition

Though overcoming the challenges of scale-up is a major benefit of continuous flow, an even more powerful advantage is its ability to not just simplify a process but to break through traditional process limitations and constraints. Frequently, a process chemist or engineer is forced to accept a less than ideal synthetic route due to infrastructure constraints, resulting in processes that can generate impurities that must be removed. In some cases, flow chemistry can provide an optimized process that reduces these impurities significantly – or even avoids them altogether.

The quality of the final product can also be enhanced in a continuous flow process because there is greater opportunity for control using real-time analysis to monitor quality, rather than waiting to measure a single batch sample. Applying PAT is generally easier in flow than with batch production, as often only temperature probes and flow meters will be needed to ensure that the process remains within the acceptable parameters to achieve product of a known quality. Where necessary, sophisticated PAT probes can be easily integrated into a flow process to allow for rapid detection of deviations. For example, layering in an additional measurement, such as Fourier-transform infrared (FTIR) or Raman spectroscopy, to track a parameter such as reaction conversion can allow real-time adjustments to correct raw material variations or drift that may be happening within the process.

Continuous flow also now makes it possible to use technologies that are technically challenging on a large scale due to infrastructure constraints, such as cryogenic conditions, Grignard reactions, and hydrogenations. Meanwhile, other technologies that are of great interest throughout the industry, notably photochemistry, are not suitable for use in a large batch reactor as a light source cannot fully penetrate the reaction mix with consistency or efficacy. However, with continuous flow, this can be achieved very easily, meaning that this technology can now be scaled up and no longer needs to be regarded as a purely academic exercise.

Every unit operation associated with traditional batch processing has a continuous flow counterpart, and the throughputs and capacities achievable with continuous flow can rival, or often even outperform, traditional batch processes. Until recently viewed mainly as a niche problem-solving technology, continuous flow should now be seen as an option when assessing a synthetic route. Indeed, continuous flow chemistry can be a powerful development tool and the process of choice.

Jonathan Knight is Market Intelligence Director and Shawn Conway is Engineering R&D Director, both at Cambrex.

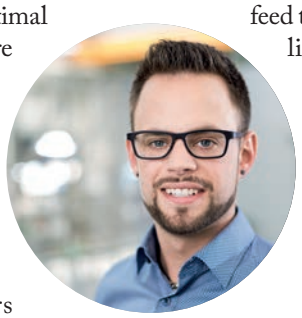
Inside the Medicine Machine

Mixing It Up

Denis Hunn from ystral takes us inside the world of the mixer, highlighting how technologies have changed over the years, offering considerations when choosing the right mixer – and giving us a glimpse of tomorrow's needs

How have pharmaceutical mixing systems changed over the years?

In the past, no matter whether producing a coating, gel or granulated product, simple propeller stirrers were used to mix solids into a liquid. There were disadvantages associated with air intake, as well as long and non-reproducible processes, and insufficient dispersion. Some problems could even lead to system shutdown in subsequent steps, such as dosing or coating. For example, if the active ingredient volatilizes during degassing or due to non-optimal dispersion, agglomerates are still present and can interfere with other equipment, such as clogging coater nozzles.



Mixing technology has, fortunately, come a long way since then. Today, it is possible to wet and disperse the powders directly via a vacuum expansion method when inducted into the liquid. Other technologies are also available, but tend to include a long dispersion time and mechanical impact, which leads to the need to then cool the process. In my view, vacuum expansion offers numerous advantages, including better product quality and reproducibility, as well as dust-free power handling. Modern mixing systems also offer shorter production times through improved efficiency and are usually easier to clean. Many systems today are designed to be cleaned in place, for example, and have other design features that improve cleaning.

What should companies consider when choosing the right system?

If you are looking for a simple mixing system, I recommend taking care to ensure that it has no free-rotating shaft because this can lead to the formation of a vortex and the impact of air. For more difficult applications, care should be taken to ensure that solids are not scattered from above into the vessel and onto the liquid surface, which can lead to the formation of agglomerates. It is always advisable to feed the two streams (powder and liquid) from opposite sides into a dispersing system to wet and disperse the powder under vacuum (as noted above). The actual batch tank does not have to be vacuum or pressure resistant for this purpose.

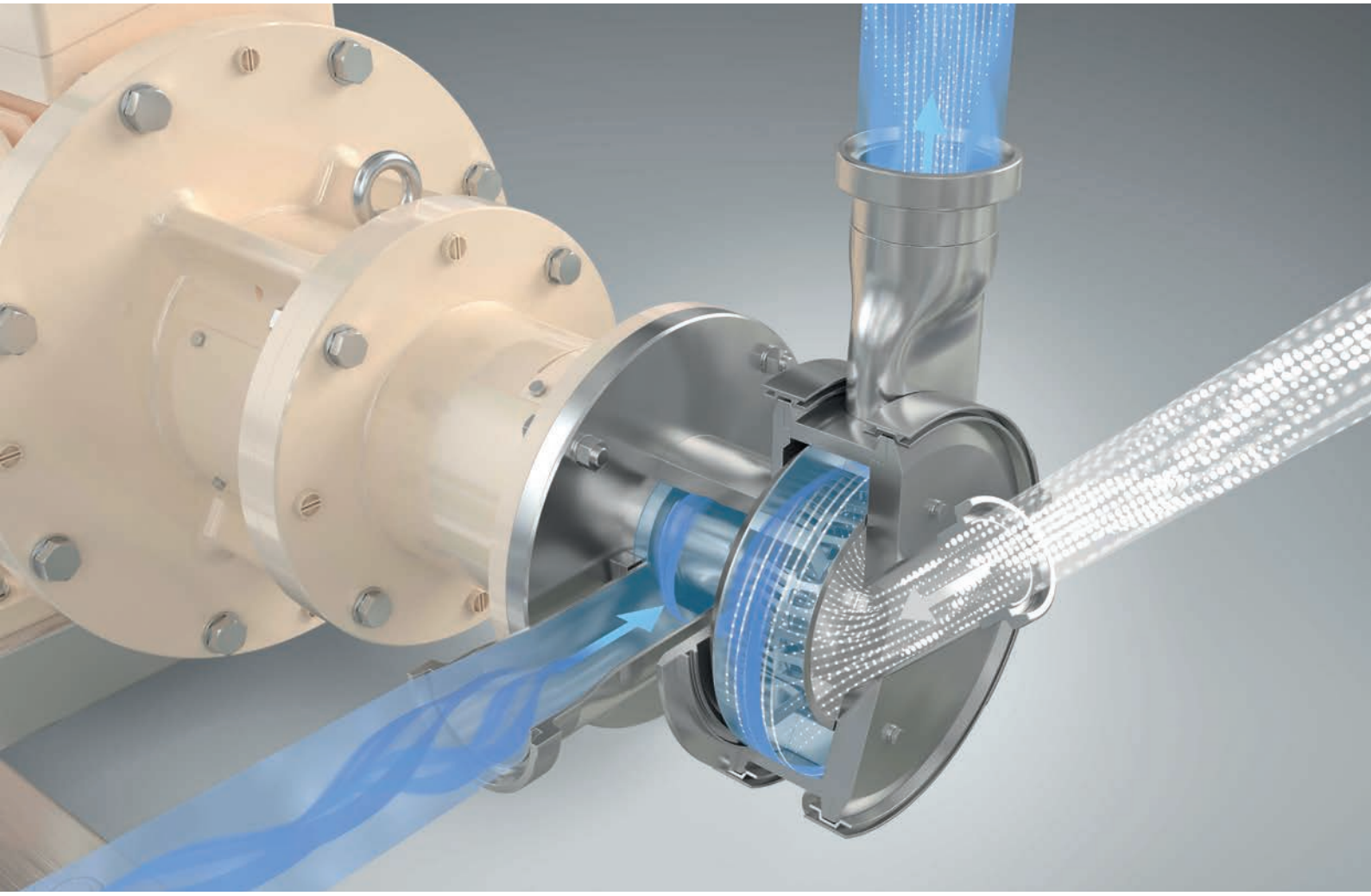
Take us inside a modern mixing machine… how does it work?

Our Conti-TDS is a powder dispensing and dispersing machine that makes it possible to remove toxic, carcinogenic, active ingredient-laden or simply difficult-to-wet powders in a dust-free and easy way. With a variety of sizes and application-specific dispersing tools, this system can cope with batch sizes from 5 liters up to several thousand cubic meters.

Put simply, the machine transports and disperses powders directly into liquids. How? By generating an extremely powerful vacuum, which reaches up to a few millibar (absolute pressure) in its dispersing zone. Powders consist of individual particles that touch one another, but there is air between these particles. The volume of air enlarges under vacuum and the distances between the particles increase. As a result, the particles are separated. The nearer the powder comes to the zone of maximum vacuum, the greater the distances between the particles. This effect can only be used in a powder flowing at high speed and under an increasing vacuum. It is precisely this effect that the Ystral Conti-TDS uses when adding powder and dispersing by vacuum. The machine transports and disperses powders directly into liquids. For this, it generates an extremely powerful vacuum in its dispersing zone so that the powder is inducted precisely into this area.

The closer the powder comes to the dispersing zone, the greater the vacuum and the faster the powder flows, which increases the distances between the individual particles. In the dispersing zone, the individual powder particles come into contact with the liquid under maximum turbulence where they are completely wetted and colloidally dispersed. Agglomerates are not created, and further dispersing is not required.

Actually, each system is tailored to the task and the local conditions on site, so we have developed a number of variations that customers can select. It is very important to work closely with customers – and I think pharma companies always find it an interesting experience to work with machine experts. We examine processes, bring in our technical know-how and are



often able to exploit potential of which our customers were not aware.

Many customers don't realize the level of care and attention that goes into building pharmaceutical manufacturing equipment. One of the biggest challenges is being able to produce equipment that can cope with both large and small batch sizes. Depending on the customer's order requirements, engineers may need to redesign system geometries and reconsider the volume of the vessel. There is a lot of thought that goes into this. Such factors are very important to the smooth and efficient running of the machine but typically go completely unnoticed by customers!

What is your advice in terms of care and maintenance of the system?

Good quality mixing machines are typically robust and built to last, but we recommend regular maintenance and careful handling; if you look after the system then there is no reason why it shouldn't still be producing products of the same quality after 30 years of use! That said, although equipment can be used for many years it is always good practice to evaluate new state-of-the-art technologies as they become available. In the pharmaceutical industry in particular, it is astonishing (even to me) that, because of validation and approval issues, legacy technology remains in use despite much more practical and significantly more efficient systems becoming available...

What industry trends will shape the development of future mixing solutions?

Right now, we are keeping our eyes on new applications in the market. Renewable organic raw materials is one key area. In addition, there is a lot of interest in the cannabis market. We have already carried out some initial projects in this field, but you'll have to watch this space for further details!

The Next Big Thing?

The Future of API Synthesis

We need to produce molecules faster, more economically and with greater control. AI and protein engineering are effective tools to help with this mission.

By David Entwistle and Oscar Alvizo

Historically, given enough time and resources, almost any small molecule API will succumb to "total synthesis" – first in medicinal chemistry and then in process chemistry. The greatest challenge facing the process chemist, both then and now, is to produce the molecules under a state of control, with a reproducible impurity profile, in an economical fashion, and at increasing scale. These seemingly simple but high-level goals arguably cause the most problems and influence route design the most. In addition, the regulatory and toxicology landscape has changed and a much more rigorous approach to impurity control, especially of potential genotoxins, has emerged (and rightly so).

More recently, the industry has recognized that it needs to be able to produce its products in a sustainable manner. For example, in almost all cases, solvent use is the greatest contributor to waste during API syntheses, which adds not only cost to the process, but also an environmental burden that must be tackled – with solvent type and usage being the main areas of concern. As drug makers increasingly seek more potent, targeted and (often as a consequence) more complex molecules, the pressure on synthetic chemists to find cost-effective and sustainable routes to their drug candidates has grown.

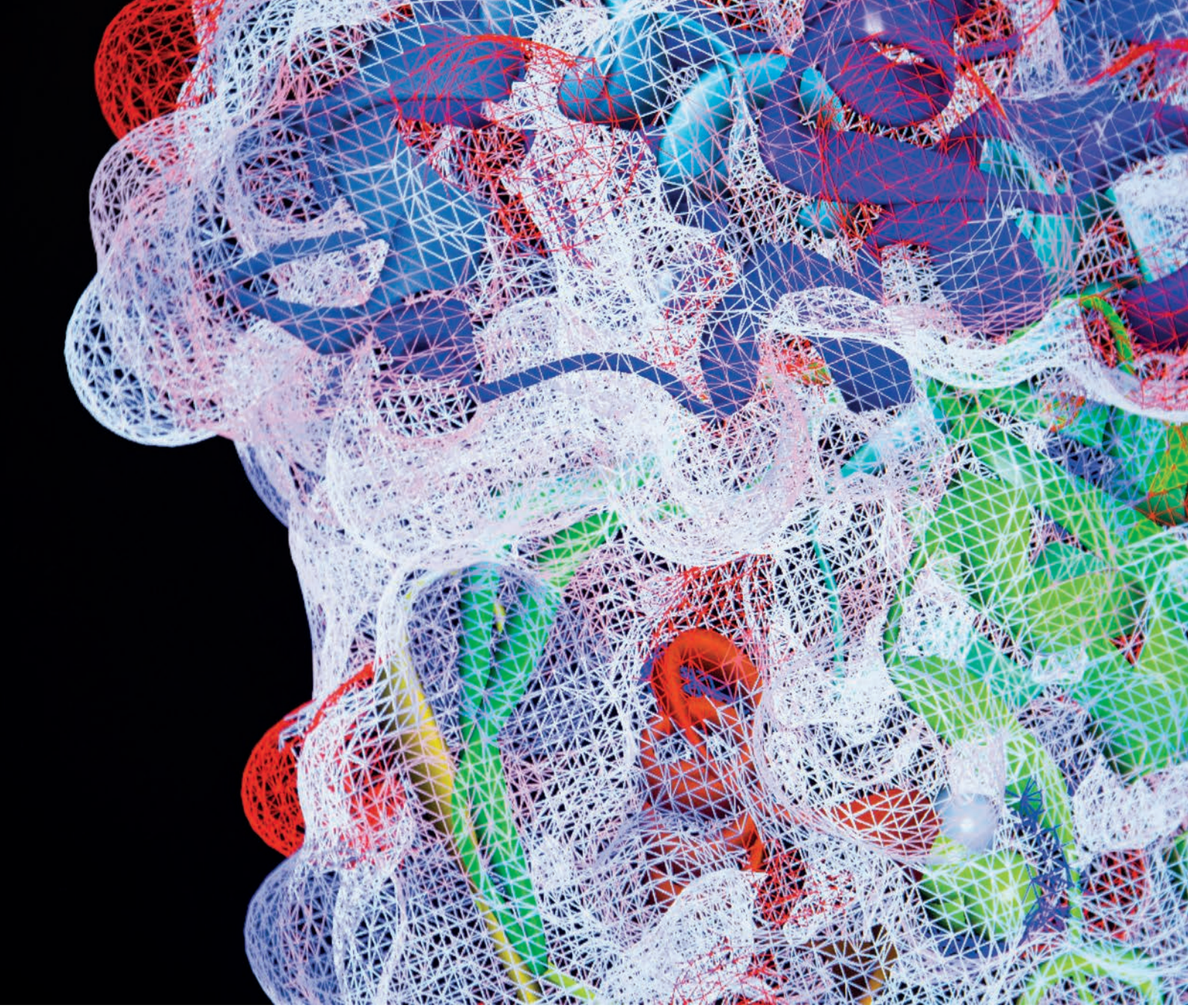
In terms of challenging chemotypes, chirality is a heavily investigated area. In the early 1990s, the FDA specified that APIs should be produced in high isomeric purity. A command that resulted in many intermediates or APIs being classically resolved, resulting in at least a 50 percent increase in the cost of raw materials, increased waste, and potential impurity issues with residual off-isomers. As asymmetric catalytic methods (both chemo- and biocatalytic) have advanced, they have become indispensable tools in producing chiral APIs.

Advances over time

Most modern pharmaceutical molecules have one or more chiral centers at which the stereochemistry needs to be controlled. Compound chirality can produce some of the biggest challenges, and the synthetic community continues to deliver exquisite methodologies to tackle these. Consider the historical progression of producing chiral secondary alcohols: originally, these might have been produced as a racemic mixture and resolved by diasteroisomeric ester formation. HC Brown's hydroboration methodology then enabled asymmetric ketone reduction, but required a stoichiometric chiral reagent. The Corey–Bakshi–Shibata system was another step forward as it used chiral oxazaborolidine catalysts and achiral, but potentially hazardous, borane complexes. After that, asymmetric catalytic hydrogenation of ketones, as pioneered by Noyori, was a powerful advance but is reliant on ruthenium, a low-abundance metal, hydrogen gas and high pressure.

Following somewhat in the shadow of many of these methods has been the use of ketoreductases. These natural enzymes have been known for a long time, but saw sporadic use in large-scale API synthesis because they were perceived as unstable in typical reaction matrices, difficult to scale, or unproductive in terms of

"The advent of directed evolution methodologies for optimizing enzymes has dramatically expanded the use of ketoreductases."



asset utilization. The advent of directed evolution methodologies for optimizing enzymes, however, has dramatically expanded the use of ketoreductases – and enzymes in general – as many of the perceived drawbacks vanish with engineered variants. Since then, highly productive processes for the manufacture of some of the world's largest drugs have been delivered – atorvastatin, simvastatin and sitagliptin, for example. The use of ketoreductases is, therefore, a good example of a methodology, enabled by directed evolution, that tackles chirality, and at the same time provides advantages when it comes to impurity generation, safety, atom economy and sustainability.

Secondly, cross-coupling methodologies, most notably the Suzuki cross coupling, have had a dramatic effect on the synthesis of APIs. The ability to control regiochemistry by selectively heterocoupling two chemically differentiated aromatic partners is immensely powerful. In recent years, concerns about the potential genotoxicity of intermediates, the use of low-abundance metals, and even the use of pre-functionalized aromatics has spurred the synthetic community to develop methods that can activate C-H bonds, or use earth-abundant metals, such as iron.

What lies ahead?

For practical, large-scale syntheses, patient safety in the form of improved control or elimination of impurities will be a considerable driver for the future. Therefore, any reaction type with dramatically improved chemo-, regio- or enantioselectivity, that does not sacrifice other key attributes, will always be of

interest. When these methods become chemo-selective enough, resulting in very low levels of impurities, it will become increasingly possible to run multistep chemical processes in single-vessel reaction cascades. This synthesis of complex molecules in just a few discrete operational steps will lead to a much better return on capital.

Methods utilizing more sustainable metals for cross-coupling chemistry will also increase in number and use in large-scale manufacturing in the future.

As mentioned earlier, sustainability is a key driver for major pharmaceutical companies. We, therefore, expect to see more and more technologies emerge that enable shorter synthetic routes and that do not depend on hazardous reagents or non-sustainable solvents. Biocatalysis, fueled by directed evolution techniques, will be increasingly deployed to heighten selectivity and increase sustainability.

Continuous or semi-continuous processing is now mainstream and will continue to expand in scope, and corresponding synthetic methods will be discovered and implemented. For example, the current resurgence in interest in methods to activate molecules in potentially non-conventional positions – for instance by photocatalysis or electrochemistry – are well-suited to continuous or semi-continuous processing. Recently, the use of photo-biocatalysis with nicotinamide dependent ketoreductases was demonstrated to provide non-natural reactivity (1). The same group has also shown that photo stimulation of flavin dependent ene reductases can impart new non-natural activity (2).

Finally, the difference between small molecule APIs and large molecule APIs has begun to blur, and improved catalytic and biocatalytic, biologic-compatible methods for processing complex macromolecules will continue to be developed.

Data and knowledge lead the way

The future of synthesis may also be affected by high-throughput experimentation and data analysis via AI algorithms. In general, efficient learning from experience provides tremendous advantages when designing novel synthetic routes, novel reagents that enable such routes, and novel processes that ultimately facilitate the implementation of such routes at scale.

"Sustainability is a key driver for pharma companies."

In 2006, we found we needed better directed-evolution methodologies to enable a manufacturing process for hydroxynitrile, the chiral atorvastatin starting material. Traditional methodologies did not yield sufficient improvements, so we introduced ProSAR, a machine-learning algorithm, to the field of directed evolution (see sidebar, Protein Engineering). At that time, the urgent need for a better enzyme on our end and the step changes taking place in the cost of DNA sequencing prompted and enabled this development. The resultant process reduced the cost of manufacture by an estimated 50 percent (3).

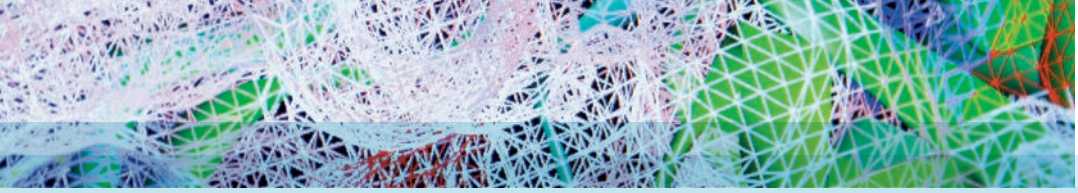
These days, data from high-throughput experimentation is the learning material that feeds AI algorithms to provide potentially improved versions of the route, reagents, and process. In our hydroxynitrile example, such datasets included structural data (enzyme sequence) and activity data from a range of different reaction conditions. For the first time, mutations that appeared beneficial for activity were also found to be deleterious for stability, and such knowledge led to the broad adoption of ProSAR, ensuring that only truly beneficial mutations were retained.

With the introduction of ever-faster analytical instrumentation and the adoption of automated screening workflows, larger and more information-rich datasets are now being generated. Databases that store the experimental information in properly structured and easily searchable form now inform and predict the experimental path for creating the desired enzyme faster and faster.

With highly targeted, high-throughput screening and machine-learning-based directed evolution, we have successfully engineered ketoreductases for commercial manufacture of a broad range of chiral alcohols, which are often key intermediates in the synthesis of pharmaceutical ingredients. Such experimental datasets for a wide diversity of compounds are now used to train AI algorithms so that the physical interactions between a substrate and an enzyme can be modelled to yield increasingly accurate predictions for new reactions.

As we continue to amass data on the substrate scope of different enzyme classes, computational tools will increasingly guide the selection of enzymes capable of catalyzing a target reaction under the required reaction conditions. Highly desirable characteristics, such as solvent stability, thermostability and pH can be deduced from previous characterizations of related enzymes using machine learning algorithms. With growing, high quality datasets and improved AI tools, directed evolution of enzymes will become increasingly rapid through more targeted computational predictions and faster decision making by the scientist.

Some companies are content with their current synthesis methods – even though they may not be the best solutions!



But the pharmaceutical industry needs better, often more chemically complex, molecules that provide increased efficacy and are safe to use. They also need to produce these molecules in an environment where tremendous societal pressure demands lower cost products. To fulfil the promise of providing more complex molecules that are produced at lower cost, innovation is required at multiple steps in the drug development process, including the medicinal and process chemistry steps.

Biocatalysis, enabled by directed evolution, is an innovation that enables the synthesis of complex molecules at any stage of the drug development process. The use of enzymes allows the development of short synthetic routes that create difficult-to-form bonds, as well as introducing chirality. These techniques are useful for the medicinal chemist, and as a candidate advances, better enzymes can be developed for ease of use, for cost, or for enabling (semi-) continuous processes. Suddenly, a lot of risk can be circumvented by making the right molecules early on, using a process that is close to scalable right from the start.

More and more companies are stressing themselves to find new ways to solve chemical manufacturing challenges and to use the power of big data to help overcome them more quickly. At the same time, these companies are engaging in partnerships to drive innovations that neither party could achieve alone. By applying the full breadth of synthetic tools available, by thinking holistically about route design from the early stages of drug discovery to the mature environment of branded drugs, and by leveraging multidisciplinary teams inside and outside their organizations, commercial chemists can implement truly disruptive innovation more readily, and with less risk and cost, than many might think.

Protein Engineering

Enzymes are immensely powerful catalysts which, in theory, allow chemists to address many of the key challenges associated with API synthesis. Enzymes have excellent chemo, regio- and stereoselectivity, and drive high-yielding, environmentally friendly processes. The enzymes themselves are sustainably produced by fermentation, are biodegradable and are generally used in aqueous media. However, natural enzymes do have limitations; for instance, their selectivity for pharmaceutically relevant substrates can be limited as these enzymes did not evolve to accept such molecules naturally.

Similarly, if the natural enzyme produces the wrong enantiomer, then the enzyme is of no use, synthetically. Natural enzymes are often inhibited by process-relevant concentrations of substrate or product, can be unstable in the conditions under which chemists would ideally like to use them and – when used in large amounts – can cause problems during work-up.

All these drawbacks can effectively be addressed by enzyme engineering. Directed evolution facilitates the rapid engineering of enzymes for the desired substrate under the desired conditions, as defined by the process chemist. This notion is hugely important; whenever an enzyme shows a trace of a desired activity, that activity can be amplified using directed evolution. From an enzyme that provided one turnover every five days, for example, directed evolution aided the development of a transaminase that is now used for the commercial scale production of sitagliptin, the API in Merck Sharp & Dohme's Januvia.

Highly selective catalysts can often enable the chemist to redesign routes, removing redundant steps and increasing efficiency. This ability to conceive of a route on paper and then make the biocatalysts perform the desired functions often has a far larger impact on productivity than simply replacing a chemocatalyst with a biological equivalent.

Furthermore, chemists aren't necessarily limited by the chemistry that nature performs. Chemists with an understanding of the mechanism of an enzyme's native activity can "hijack" it and modify it to perform a new transformation, such as repurposing cytochrome P450 monooxygenases to perform cyclopropanation, as Nobel Laureate Frances Arnold did. The key realization is that the novel activity seen initially can be extremely low, yet measurable, and then through directed evolution, be escalated to the desired activity for synthetic use.

David Entwistle is Director, Process Chemistry, and Oscar Alvizo is Director, Computational Biology, both at Codexis.

References

1. *MA Emmanuel et al., "Accessing non-natural reactivity by irradiating nicotinamide-dependent enzymes with light," Nature, 540, 414–417 (2016).*
2. *KF Biegasiewicz et al., "Photoexcitation of flavoenzymes enables a stereoselective radical cyclization," Science, 364, 1166–1169 (2019).*
3. *SK Ma et al., "A green-by-design biocatalytic process for atorvastatin intermediate," Green Chem., 2010, 12, 81–86 (2010).*

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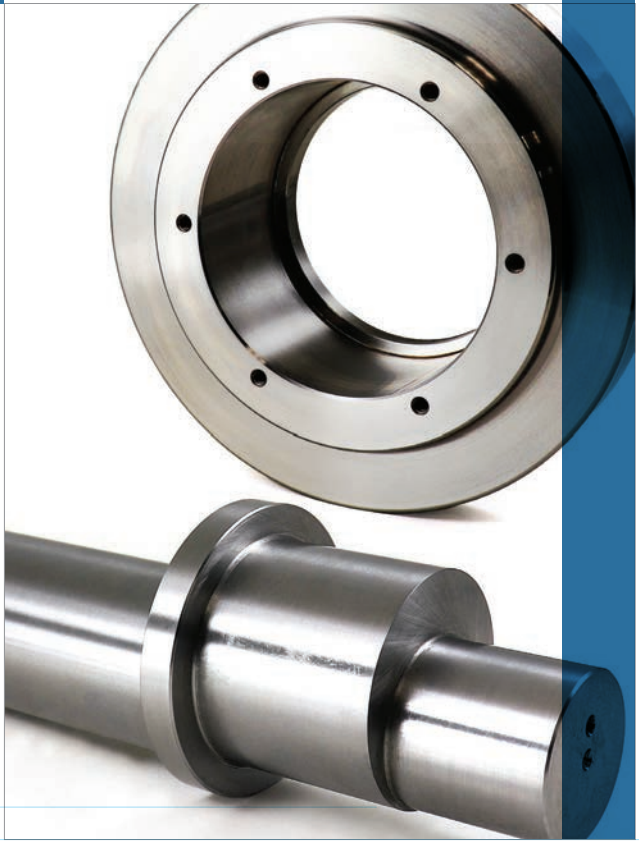

The Importance of Access

Sitting Down With... Chip Davis, President and CEO of the Association for Accessible Medicines (AAM).

What does the AAM do – and why are you so passionate about its cause?

The Association for Accessible Medicines is a Washington DC-based trade association that represents generic drug and biosimilar manufacturers. We advocate for policies to ensure that patients have access to safe, effective and affordable medications. Our members are manufacturers, and we regularly engage with them for policy and legislative proposals regarding healthcare and prescription drug costs, and FDA issues. We start from the premise that no medicine is effective if patients cannot access it.

For me, it has always come down to the importance of patient access. I am a true believer in the value the pharma industry provides – both in terms of new medicine development and the competition among manufacturers that increases overall accessibility and affordability.

Why did you choose to take on the role at AAM?

In early 2015, I was contacted by the AAM (known then as the Generic Pharmaceutical Association) as part of their global search for a new CEO. I had been in the industry for about 20 years at the time, but all my experience had been on the branded side, and it didn't seem like an obvious fit.

That said, when I sat down with the Association board, I was immediately struck by their desire to increase the sector's visibility and relevance in the public policy debate. Now, as a result of a lot of hard work and dedication by our members and our team here at AAM, the generic industry and biosimilar sector are poised at the crossroads of innovation, accessibility and affordability. That makes this a great industry to represent.

What challenges face those seeking to ensure access to affordable (generic) medicines?

There are three major challenges affecting patients' access to affordable medicine. The first is the supply chain. Generics are supposed to win by functioning effectively. They essentially serve as a commodities market, and such markets need many buyers and sellers to operate efficiently. However, the last two decades of buyer consolidation in the US have led to just three wholesalers now controlling about 90 percent of the generics market. That consolidation has been a major factor in driving generic prices down over the last several years. On one hand, this can be deemed a positive, but if prices in the US market are deteriorating to levels at or below the cost of manufacture, we run an increased risk of drug shortages and reduced competition as individual manufacturers choose to exit certain markets.

Number two is the increased aggression by certain product originators. They may deny selling legitimate drug samples to a generic manufacturer to prevent necessary research and testing to file a drug application with the FDA and ultimately bring a competitor to the market. In addition, increasingly in the US we are seeing generic drugs listed on insurance plan formularies requiring either the same or even a higher copay or co-insurance than the more expensive brand-name drug. In such cases, why would patients ever want to switch to the less expensive medicine, when in actuality it is not less expensive to them? And over time, if this practice of preferring a branded drug to a generic on a drug formulary continues, generic manufacturers will reassess whether to continue developing medicines designed to increase access and lower costs, if those lower costs are not being realized by patients.

The last area of concern is the political and policy environment. There's a lot of understandable anxiety and agitation about drug costs among all stakeholders. Ironically, the majority of prescription drug costs in the US have been dropping while worries over rising costs have increased and it's created a challenging environment where leaders in government may come to think that generics are somehow responsible for increased drug costs, when the exact opposite is true.

Of which AAM successes are you most proud?

When I started with AAM, I knew the industry wasn't necessarily satisfied with its voice and relevance in the public policy debate. The data showed that generics constituted an overwhelming percentage of total prescriptions for a very small amount of total costs. We had a lot of important communication and messaging work to do. Over the past four years, we've been able to secure Administration and Hill buy-in to the fact that generics are an essential part of any solution to control drug costs, particularly specialty drug costs.

In 2017, we had an extremely important victory in the reauthorization of the generic drug and biosimilar user fee agreement – a major factor in ensuring the FDA has the resources to conduct timely reviews of generic and biosimilar applications. And with regard to drug samples being denied to generics makers, we're confident that our recommendations will be part of the policy solution if Congress passes reforms. Likewise, manufacturer competition is gaining traction as an issue on Capitol Hill.

Who's had a major influence on your career?

I've had a number of mentors in my life, starting with my father. I'm his namesake, and I've always felt he was the greatest man I've ever met. Among many business leaders and industry CEOs, one that comes to mind is David Brennan – the CEO of AstraZeneca when I worked there. He taught me to balance the commitments of running a successful business while also seeking to advance patient access to medicine. I've been exposed to many successful people in my career, and I am currently surrounded by so many I am fortunate enough to call colleagues at AAM. When you get to see them perform like I do, it's very motivating.

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