

# the Small Molecule Manufacturer™

## Upfront

Fighting counterfeits  
with edible tags

08

## Business

How to take advantage of  
the small molecule pipeline

18 – 20

## Inside the Medicine Machine

What are the benefits of  
hot-melt extrusion?

22 – 24

## Sitting Down With

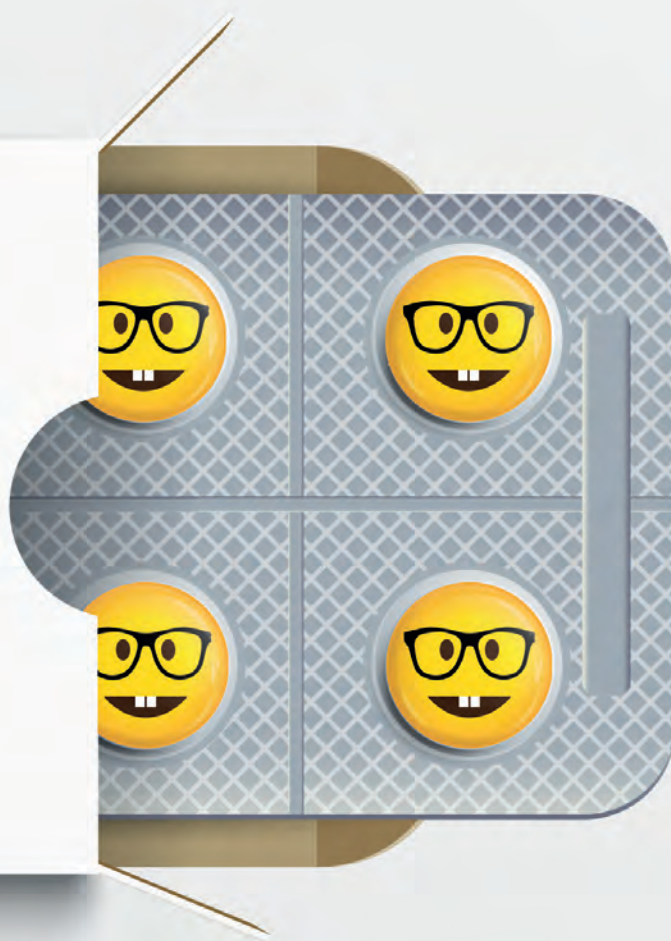
An innovative mind,  
Mike McMullen

26 – 27

## An Intelligent Approach

What advantages do smart  
packaging options offer to both  
manufacturers and patients?

10 – 16





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Disease outbreaks attract enormous media attention. Some of this attention is positive, leading to raised awareness, education and vigilance. Unfortunately, many media outlets appear to revel in spreading fear and panic with terms like “killer disease” – or they publish ridiculous stories about individuals in countries like the UK hoarding face masks and refusing to use public transport or socialize for fear of catching the disease.

The pharma industry is already preparing its counter offensive against the virus, with companies like Janssen, Sanofi and Inovio all working on vaccines. But the industry must also protect the rest of its patients, by keeping a close eye on supply chains and the potential for medicines shortages caused by disruption in China.

China is a huge contributor to the world of medicine manufacture, particularly in the small-molecule space. India, for example, is said to import around 70 percent of its API requirements from China (1). And a huge proportion of the US’ supply of antibiotics and 95 percent of its ibuprofen are made in China (2). Prices of some key medicines are already reported to be on the rise in India following the outbreak (3). China is also a key supplier of excipients and other ingredients, as well as many lab and manufacturing consumables.

The FDA says it is “keenly” aware that the medical product supply chain will be disrupted – and the agency is already in contact with hundreds of drug manufacturers to monitor the situation. But manufacturing disruptions are not the only source of shortages; panic buying compounds the issue – and the FDA is already tracking reports of increased ordering through distributors of medical devices and medical personal protective equipment. Other agencies and governments worldwide are also keeping a close watch on the situation, particularly when it comes to medical supplies.

This health emergency isn’t the first faced by the pharma industry and health authorities – and it won’t be the last. Important lessons have been learned from previous outbreaks, such as Ebola, SARS and swine flu. Let us hope these serve us well in bringing the coronavirus under control as quickly as possible.

Stephanie Sutton  
*Editor*

*Stephanie Sutton*

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1. *This Is Money*, “Indian generic drugmakers may face supply shortages from China if coronavirus drags on,” (2020). Available at: <https://bit.ly/38TVCLn>.
2. *BioWorld*, “Coronavirus outbreak in China sparks fears of disruption for global drug supplies,” (2020). Available at: <https://bit.ly/3a26qH8>.
3. *The Times of India*, “Paracetamol prices up 40% as coronavirus shuts China,” (2020). Available at: <https://bit.ly/2uorGYA>.



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- 03 **Editorial**  
Protecting Global Health  
by Stephanie Sutton

## Upfront

- 06 The latest news, views  
and research.

## Feature

- 10 **The Smart Approach**  
From Bluetooth tech to  
temperature sensors, smart  
packaging is bringing new  
benefits for both manufacturers  
and patients.

## Business

- 18 **Small Molecules, Sizable  
Market Opportunities**  
Stephan Haitz analyzes the  
trends in small molecule  
manufacturing, including  
the role of small and virtual  
companies, as well as CDMOs.



## Report

- 21 Designed With You in Mind

## Inside the Medicine Machine

- 22 **Exploring Hot-Melt Extrusion**  
Why should manufacturers  
consider hot-melt extrusion?  
And how can mathematical  
models help with scale up?

## Sitting Down With

- 26 **Mike McMullen, President and  
CEO, Agilent Technologies,  
Santa Clara, California, USA**

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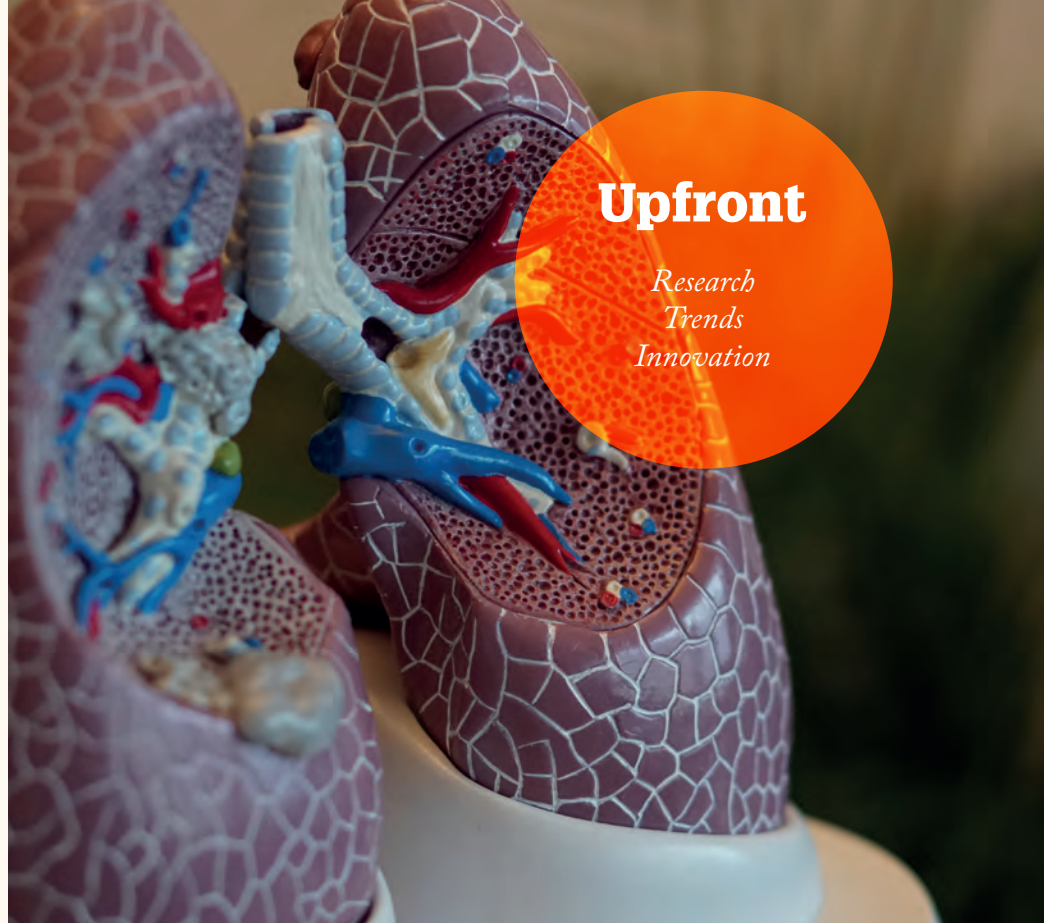
## A Breath of Fresh Air

### Can repurposed drugs improve treatment options for patients with cystic fibrosis?

The Cystic Fibrosis Foundation has awarded a \$692,000, two-year contract to Calibr, the research and development arm of Scripps Research. Calibr's ReFRAME – a library of over 13,000 small-molecule drugs with proven track records of safety in humans – will be used to identify existing medicines suitable for treating infections caused by *Burkholderia cepacia* complex, which comprises 22 bacterial species.

According to Arnab Chatterjee, Vice President of Medicinal Chemistry at Calibr, CF remains one of the hardest and most complex diseases to treat – partly due to the number of organs and tissues affected by the lack of a functional cystic fibrosis transmembrane conductance regulator protein.

The *Burkholderia cepacia* complex poses a serious health risk to patients with CF because the bacteria can cause *cepacia* syndrome, a life-threatening systemic infection. It also often causes patients to be rejected for lung transplantation.



The team will cultivate bacteria to imitate the infection environment triggered by *B. cepacia* and use the ReFRAME library to select molecules with antimicrobial activity.

“Many of the bacterial species that are problematic in CF are resistant to currently available antibiotics. Our approach could also be applied to other bacteria relevant to CF, such as *Pseudomonas aeruginosa*, bacteria which cause chronic inflammation and lung infection in CF patients,” Chatterjee explained.

The Calibr researchers are also working with John LiPuma, a Professor at the University of Michigan, who works closely with CF patients. LiPuma, whose laboratory maintains an extensive culture collection that includes approximately 35,000 strains of respiratory tract bacterial pathogens, will provide patient samples and help the Calibr team accelerate the translation of anti-infective candidates.

The Cystic Fibrosis Foundation has committed to invest \$100,000 million to CF research through its new “Infection Research Initiative” between 2019 and 2033.

## INFOGRAPHIC

### Out at SEA

A survey asked 45 pharma execs what the key challenges and opportunities were for the Southeast Asian (SEA) region in 2020 and beyond

#### Future aspirations

Annual revenue growth in the Southeast Asian pharma market is predicted to exceed

**11%**  
over the next 5 years

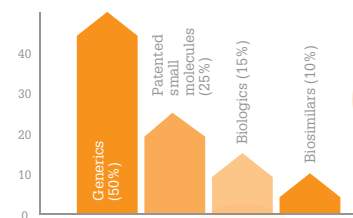
With expected sales of

**\$40bn**

IN 2020

#### Potential for growth

Which product classes have the best growth opportunities in the SEA region?





## BUSINESS IN BRIEF

*Fines, approvals and anniversaries...  
What's new in business?*

- GSK's decision to delay the market availability of paroxetine, an antidepressant, could be considered anti-competitive, Juliane Kokot, a legal advisor to the European Court of Justice (ECJ) has warned. The company was previously hit with a £37.6 million fine in 2016 for the "pay-for-delay" deals it had cut with generic companies.
- Novo Nordisk's blockbuster drug, Ozempic, a medication that stimulates insulin production in Type II diabetics, has won extended label approval from the FDA. The expansion was granted due to the drug's ability to treat cardiovascular disease, non-fatal heart attack and non-fatal stroke in patients living with Type II diabetes.
- The European Medicines Agency (EMA) celebrated its 25th anniversary on January 27. Guido Rasi, the EMA's Executive Director, commended the work of the agency in a recent statement: "25 years is a significant milestone for EMA. Together with our partners



and stakeholders from national authorities, EU institutions and civil society, we harmonized and improved medicines' evaluation, stimulated innovation, improved safety monitoring and management, fostered transparency and dialogue, built relationships with international partners, and helped to make medicines accessible to those who need them."

- Colorcon has received an EXCiPACT GMP and GDP Certificate from SGS, one of EXCiPACT's internationally recognized certification bodies. The certificate was awarded to Colorcon for its Westpoint site in Pennsylvania, US, for its capacity to manufacture and distribute lake pigments (wet and dry) and polyvinyl acetate phthalate (phthalin-coating materials) for use as pharmaceutical excipients.

## Best-in-Class Packaging

**Electronic locking features and a child-resistant design cinched the "Best Innovation in Drug Delivery Device" award at Pharmapack 2020**

At the recent Pharmapack 2020 event, Nemerica picked up the "Best Innovation in Drug Delivery Device" award for Safe'n'Spray, which features child-resistant features (fingerprint identification) and a reusable electronic locking unit to prevent overdose. Nemerica's device can also be integrated with a cloud platform that shares treatment management and statistical analysis of user-behavior with patients, healthcare professionals, and pharma companies.

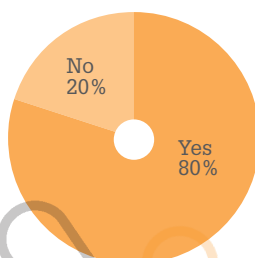
"Not only does Safe'n'Spray help protect vulnerable patients though its electronic features, its production isn't an inconvenience to manufacturers, as existing filling lines can be used for its assembly," says Marc Hämel, Nemerica's CEO.

Other winners at the event included Credence MedSystems, Huhtamaki Flexible Packaging, and Rondo.

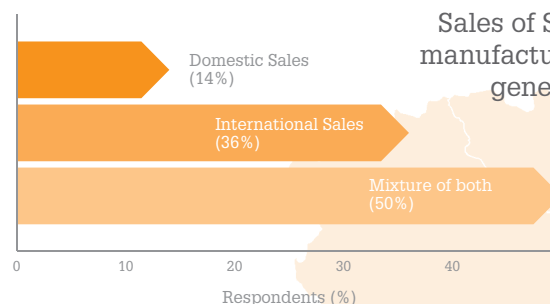


## Generics

Will government price controls and the availability of generics lead to and increase in domestic manufacturing capabilities in the next 5 years?



## Sales of SEA manufactured generics



Source:  
CPhI Insights, 2020.  
Available at: <https://go.aws/2vn0klZ>

## Security You Can't Beat (But Can Eat)

### Combating counterfeits with edible tags

Researchers at Purdue University hope to stop drug counterfeiters in their tracks by adding edible security tags onto tablets (1). Despite efforts to use distinct markings, colorings and shapes to deter counterfeits, fake drug manufacturers are still able to infiltrate the market. The problem with current authentication techniques, according to the recently published paper, is that “they are symmetric” – if counterfeiters have access to the same techniques, they are easily replicated. Edible security tags are an advanced anticounterfeiting solution that provide “asymmetric” on-dose authentication down to the individual tablet.

The approach works by applying the concept of physical unclonable functions (PUFs), which were originally developed for hardware security, to the surface of drug capsules and tablets. Like fingerprints, each PUF is unique. When a LED light is shone on the tablet, the tag produces an unpredictable, random pattern. Digital bits can be extracted

from an image of the patterns to produce a security key, which can be used to confirm the authenticity of the drug.

A smartphone app, currently under development, will allow patients to take a picture of the pattern developed by the tags and identify if the medicines are genuine or fake.

The Purdue team translated the PUF concept to pharmaceuticals by using silk proteins and fluorescent proteins, which are flexible and can be easily digested. “In our initial trial, we attached the PUFs to the surface of capsules. Their flexibility means that they can be attached to flat or curved surfaces but they can also be integrated into tablets during the manufacturing process,” explained Young Kim, an associate professor at Purdue’s Weldon School of

Biomedical Engineering.

The tags can also be developed to hold information about dose and expiration. Initially, the tags could only last for two months before degrading. Since then, however, the team has improved the quality of the tags.

“The security tag proteins will remain in good shape so long as they are stored in robust packaging,” Kim explained. Jung Woo Leem, another researcher on the team said, “Our current goal is to ensure that the protein tag lasts as long as the medicine does – and that they don’t affect the quality of key ingredients.”

#### Reference

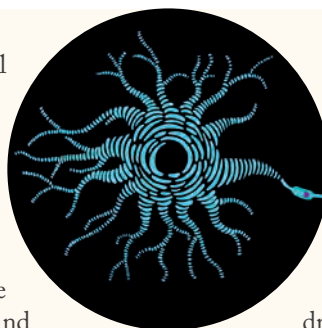
1. JW Leem et al., *Nature Communications* (2020). Available at: <https://go.nature.com/31Ae2bh>

## Slowing the Pace of Parkinson's

### Researchers explore a small molecule with the potential to tackle disease progression

A team, led by Matthew Disney from Scripps Research and M. Maral Mouradian from the Rutgers Robert Wood Johnson Medical School

Institute for Neurological Therapeutics, has developed a small molecule drug, dubbed Synucleozid, which targets the messenger RNA (mRNA) of  $\alpha$ -synuclein, a protein whose misfolding is genetically and neuropathologically linked to Parkinson’s disease (1). Though there are several experimental treatments in development that target  $\alpha$ -synuclein



protein aggregates, the team’s goal is to prevent them from developing entirely by inhibiting its translation at the mRNA stage.

Disney and Mouradian are now optimizing the drug so that it can be applied to other neurodegenerative diseases.

#### Reference

1. MD Disney et al., *PNAS*, 1457-1467 (2020).





## IMAGE OF THE MONTH

*Tracked and Traced*

A French CDMO, Skyepharma, has collaborated with SEA Vision to ensure the complete serialization and aggregation of systems on its packaging lines.

Credit: SEA Vision

Would you like your photo featured in Image of the Month?  
Send it to [maryam.mahdi@texerepublishing.com](mailto:maryam.mahdi@texerepublishing.com)

## QUOTE of the month

*"I believe that together we can produce breakthrough therapies to overcome the challenges in antibiotic research, but also fear that a 'go it alone' approach will stop the industry finding the new therapies we urgently require."*

Steve Arlington, President of The Pistoia Alliance, on antibiotic resistance. [www.pistoiaalliance.org](http://www.pistoiaalliance.org)

## Waste Not, Want Not

**Which techniques best remove residual pharmaceuticals from wastewater?**

Researchers from the University of Buffalo and the Stony Brook University School of Marine and Atmospheric Sciences have identified two techniques – ozonation and the use of granular activated carbon — as being most effective in removing pharmaceuticals from wastewater (1). The techniques were shown to be able to remove up to 95 percent of drugs, including antibiotics and antidepressants. The widespread presence of pharmaceuticals in water sources has been a long-held concern for many within the scientific and environmental communities.



They are now turning their attention to addressing the secondary effects of using the wastewater treatment plant (WWTP) techniques they investigated. For example, it's possible that ozonation may introduce new compounds, including degradation by-products of pharmaceuticals.

### Reference

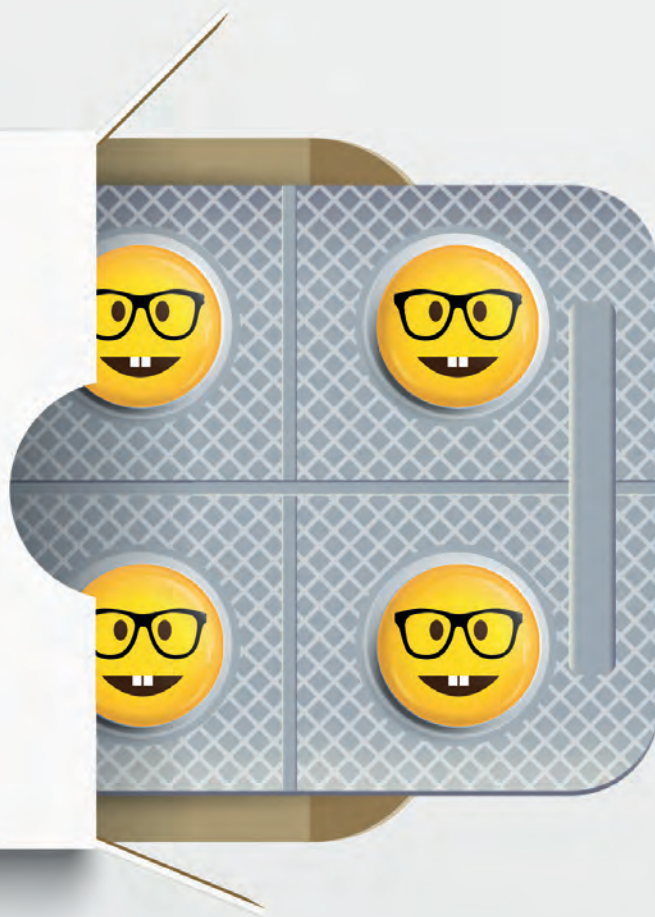
1. DS Aga et al. *Environmental Science: Water Research & Technology* (2020).

# *the* **SMARTER,** *the* **BETTER**

From improved supply chains to improved adherence, we explore how smart solutions can transform packaging – and the patient experience

By [Maryam Mahdi](#)

The pharmaceutical supply chain is notoriously fragmented – with repercussions for those who engage with the industry. Helping to bridge the gaps that have rendered the supply chain sluggish and vulnerable to counterfeiting are smart technologies, which offer suppliers, companies and patients the opportunity to access key data about product shelf-life, temperature, and dose frequency. Here, we speak to five industry experts who define smart packaging, address the challenges in bringing smart solutions to market, and predict what the future holds for this new area.



## *Featuring:*

Clockwise: [Josh Stein](#), President and Cofounder, AdhereTech; [Alex Cole](#), Senior Strategic Marketing Manager, CPI; [Ward Smith](#), Director of Marketing & Business Development, at Keystone Folding Box Co.; [Mark Roemers](#), Chief Executive Officer, AntTail; [Steve Tallant](#), Senior Director, Solutions Marketing Group, Systech.



## *What does smart packaging mean to you?*

*Alex Cole:* Packaging has two functions. The first is to protect the goods inside the package, the second is to communicate information. These two functions are important all along the supply chain and the communication function can, for example, include instructions on how to handle the package (for the logistics companies) or show what's inside the package (for the consumer). Smart packaging is an extension of these traditional functions that adds extra features that are chemical-, digital- or electronics-based, providing better protection of goods (active packaging) or enhanced communication and sensing (intelligent packaging). Smart packaging has the potential to shift packaging from a necessary cost to something that is providing added value.

*Steve Tallant:* Smart packaging encompasses many things, so giving it a clear-cut definition is a challenge. I think of it as “connected” packaging. This concept could mean an additive digital tag, or leveraging serialized barcodes and smartphones

to create the connected package. Smart packaging transforms packaging into something much more useful for both the supply chain and for patients.

*Ward Smith:* For the past 50 years, the traditional pill bottle has offered no benefit in terms of prompting the patient to better adhere to their dosing regimen. Drug packaging provides a unique opportunity to provide a touchpoint to patients each time they see a product, so improving packaging design using smart or intelligent features, which can capture and communicate patient behavior to healthcare providers, should result in improved patient outcomes and help alter patterns of patient adherence for the better.

*Josh Stein:* A large number of patients do not take their medication as prescribed. Non-adherence is widely regarded as the biggest problem for the healthcare sector and can result in significant medical repercussions and financial consequences. This is a very complex problem with many aspects to take into account.

As Ward said, smart packaging helps support patients and improve rates of adherence. They can also improve the industry's



distribution of medicines. Simply put, smart packaging is helping to seamlessly connect various aspects of the pharmaceutical industry and put the spotlight on the needs and behaviors of patients.

*Mark Roemers:* Smart packaging allows for a more efficient supply chain that produces less waste. It allows for data completeness, a key component in ensuring the quality of a medicine at any point in the supply chain. At each stage of a product's lifecycle, using the technologies we've developed, we are able to monitor the temperature of products shipped and stored via both internal and external shipping lanes which has benefits not only for pharma companies and their suppliers, but also patients – the end-users and recipients of these products.

### *In what ways are companies benefiting from smart packaging?*

*Tallant:* Smart packaging represents a new avenue for companies when it comes to product authentication. Despite being introduced to prevent counterfeiting, serialized barcodes are actually easily fabricated and copied. The new generation of emerging digital tools, such as e-fingerprinted barcodes, creates a closed loop of trust for the drug manufacturers and packaging suppliers. Simply put, pharma companies are benefiting because any given product can be authenticated anywhere in the supply chain. Counterfeits can be detected immediately without having to send samples back to a lab for evaluation.

*Roemers:* As Steve pointed out, smart packaging allows for data completeness, and therefore a more transparent supply chain. The pharmaceutical supply chain has gained a reputation for being long and fragmented, making it vulnerable to counterfeiting – as well as issues like temperature variation. What use is a spoiled or fake medicine to a patient?

With smart technologies, like Bluetooth sensors, it is now possible to combine data relevant to different stakeholders within the supply chain to ensure the quality of products by logging temperatures and alerting the relevant parties if changes happen so that corrective measures can be implemented.

*Smith:* In my view, smart packaging can also enhance phase I and II clinical trials by giving pharma companies access to accurate patient data through monitoring devices. And that means the industry can move away from relying on self-reported dosing histories, which have been shown time and again to be a source of inaccuracy in trials. Patients have to rely on memory when filling out diaries with dosage history, but emerging technologies can remind patients when each dose was taken and prompt them to take missed doses before too much time has elapsed.

### *And what about patients?*

*Cole:* Smart pill packs, smart bottles and other related technologies can support higher adherence levels. My mother is an example of a patient who has had difficulty in using conventional packaging. She recently had a stroke and lost some of her eyesight. When she left hospital, she was given three packs of pills and verbal instructions – “take one of these in the morning, this one at lunchtime and this one in the evening. The instructions are written on the packs”.

When she left the hospital, she asked me, “when do I take these?”. I had to then write in really big letters on each of the packets when each should be taken. Then I helped her program reminders in her phone to alert her when it was time to take the medicine and which one. Imagine a smart packaging system that does all this for you; it knows when a medicine has been taken out of the pack and reminds you if you haven't taken it. It can also connect with verbal instructions or patient information leaflets to help the patient understand what they are taking – which is significant when you have a patient with poor eyesight.

There are other elements of smart packaging that can help patients too. For example, when you first start using an inhaler, it's hard to learn how to breathe in the medicine correctly. If you have a smart device that is either the actual inhaler or a training device, it can tell you if you're taking it correctly or train you to do so.

*Tallant:* Smart packaging ensures that patients are consuming legitimate medicines for their conditions and once connected, as Alex pointed out, they can also discover additional materials the manufacturer deems important to provide, receive notifications, and feel more supported in their medical adherence.

By enabling engagement and information dissemination, better relationships are created between patients and the products they use – and that definitely helps create a more positive perception of the pharmaceutical industry.

*Roemers:* Sensor technologies can also give pharmacists and other healthcare providers information about the ways medicines are stored in patients' homes. We call this “last mile monitoring.” For example, when patients pick up their medications from pharmacies, they can receive them in sealed bags that have our sensors in them. Information about storage conditions is then fed back to us via gateways (similar to routers) or smartphones. Upon completion of their course of medication, patients can receive automatic evaluation detailing their compliance, the quality of their medication and whether storage conditions were adequate.

*Smith:* The adoption of smart packaging with commercial Rx products would definitely help improve the public perception

of the pharma industry and offer the best chance for patients to dose properly with medication in an ongoing way. Patients would likely better understand the links between drug adherence, the regimen's efficacy, and their overall health. And it would become all the more obvious that drug manufacturers have their health interests at heart.

### *What medicines benefit most from smart packaging?*

*Tallant:* All medicines will ultimately benefit. But the immediate targets are high-value medicines, as well as highly diverted and counterfeited drugs like opioids. Medicines destined for non-serialized markets will be another important target for the industry too. In the developing world, WHO has stated that, in some markets, over 50 percent of drugs can be counterfeit. Allowing end-users to leverage a smart package for authenticity detection would help save lives.

*Cole:* I think it depends on the function of the smart packaging. If the function is to improve adherence, then all medications stand to gain. But because developing novel packing solutions comes at a cost to companies, the added value must be measurable; it could be the value to the pharma company from patients refilling their prescriptions more often, or perhaps the value to patients, who have better clinical outcomes due to taking medicines correctly. From a patient point of view, it can be hard for them to see the benefit of prophylactic medicines, such as some inhalers, so smart packaging that offers support and reminders in accordance with the doctors' instructions can give long-term benefits to patients.

If the function is environmental monitoring, then temperature or environmentally sensitive medications will be perfect candidates. Notably, cold chain medicines account for 75 percent of biologics, and between 10 and 15 percent of small molecules. Using smart packaging for environmental monitoring can reduce supply chain losses, and can be performed down to the granularity of individual bottles, vials or boxes of medication. The data can be used to understand if medicines have remained within the correct environment throughout the supply chain and to learn where supply chain losses are happening.

### *What are the regulatory challenges?*

*Stein:* From concept to completion, there are multiple regulatory challenges for smart packaging R&D. The laws are stringent (with good reason!), but ensuring that a product meets the requirements of federal regulators, pharmacopeia and medical packaging laws, state laws, and the requirements

## *Intelligent Innovators*

### What role does your company play in pharma packaging?

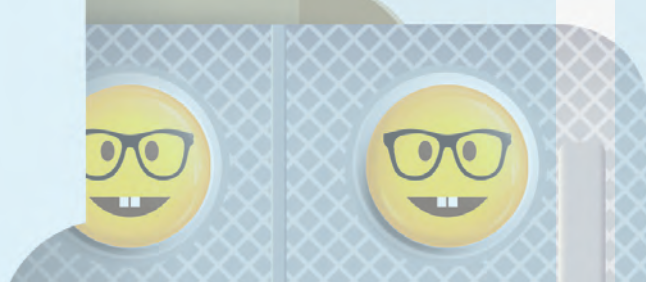
*Steve Tallant:* Systech has been involved with pharmaceutical packaging for over 30 years. Our main focuses are serialization and compliance. We help customers turn serialized barcodes into active digital e-fingerprints. We believe that everyone, from consumers to patients to physicians, have the expectation that the things they interact with on a daily basis will have some form of digital capability.

*Alex Cole:* The opportunities offered by digital technologies and the internet of things offer significant benefits for patients and pharmaceutical companies, but how can this technology be applied to packaging, what are the benefits and how can the business case be fully evaluated? CPI is a UK government-funded research organization, which has the capability to design and manufacture smart and connected packaging, in volumes that will help companies apply, test and understand the benefits of these technologies. CPI has manufacturing-scale equipment and expertise, which is today being used to integrate electronics into packaging products and help develop the supply chains needed to bring this novel technology to fruition.

*Mark Roemers:* AnfTail is working to address issues that have riddled the pharmaceutical supply chain for far too long. We design, develop, and deliver products and services to monitor and track the origin and temperature of medicine in the temperature-controlled supply chain. Temperature is a key factor in ensuring the quality of a medicine and guaranteeing that regulatory standards are met. More often than not, medicines are exposed to freezing temperatures and are at risk of spoiling due to their insufficient monitoring when shipped. Through our smartphone and gateway applications, we aim to empower professionals in the supply chain by giving them the information they need to safeguard product quality so that patients receive the medicines they deserve.

*Ward Smith:* Keystone designs and manufactures paperboard packaging for oral solid dose prescription products, clinical trial study drugs, over-the-counter products, injectables and medical devices. We also focus on developing child-resistant and senior-friendly packaging as well as packaging solutions that promote medical adherence.

*Josh Stein:* AdhereTech is a provider of smart medication containers and digital support that connect patients to care, with clinically-proven results. At AdhereTech, we aim to improve the patient experience through user-centric packaging design. Our customers include many large pharmaceutical manufacturers for multiple specialty medications - and products are distributed from nearly all top specialty pharmacies.



## Enhancing Adherence

By Stefan Wiedemann, Senior Director of Strategic Marketing and Business Development at Schreiner MediPharm, a business unit of Schreiner Group

Medication non-compliance is a growing concern in the healthcare sector. Various studies examining this issue in recent years have confirmed the following problem: if the majority of research outcomes are correct, and more than 50 percent of patients do not take their medications as prescribed (1), the economic and personal costs of inadequate patient adherence are enormous. In the US alone, the costs of medical non-compliance for the healthcare sector are estimated to range between \$100 billion and \$290 billion annually (2). Furthermore, approximately 125,000 deaths and more than 10 percent of hospitalizations per year in the US are directly linked to non-adherence (3). The obvious adverse effects on public and private healthcare systems, therefore, directly and adversely impact on the profitability of pharmaceutical manufacturers.

A variety of different technologies can be used to track medical adherence. eDiaries, apps which document patient behavior or make use of integrated camera and video detection to help capture the medicine intake, have been available on the market for some time. Advanced technologies, such as special sensor pads that detect the intake of edible micro-ingredients, are also in development and underline the importance of smart technologies

as enablers for the collection of adherence data. The megatrend towards digitization is also a key driving force behind smart packaging, combining printed electronics and hardware components for diverse applications and types of packaging, such as blisters, multi-dose wallets, trays, boxes, plastic bottles, pens and syringes. State-of-the-art smart blister wallets, from a usability point of view, are designed so that patients do not necessarily recognize the smart features they possess. For instance, they are equipped with printed and hidden conductive lines connected to small electronic units with their own power supplies that receive signals when conductive circuits are interrupted. If these circuits are flexible and robust, they can easily be customized to pharmaceutical product packaging. The printed circuits do not increase the push-through force on the cavity level, which offers patients a familiar tactile experience. Whenever a pill, vial or syringe is removed from its packaging, the corresponding compliance data (for example, whether the medication was taken at the right time and in the correct quantity) is generated and stored automatically in the integrated circuit. Existing blister designs and the number of cavities can be adapted, which guarantees a tight sealing process with few adjustments to existing production equipment.

Bottles can also be equipped with smart technology. In addition to bottle caps that recognize the date and time when a patient opens a vial, modular smart necks can be attached to bottles after the filling process. Customizable to various bottle sizes and shapes, these smart electronics can detect

every instance of pill removal. They also track if and when a pill is put back – in case it has accidentally dropped out of the bottle – allowing for permanent monitoring of the actual number of remaining pills. This could also provide a link to automated re-ordering processes.

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of both pharma and pharmacies – makes for an extremely complex environment. Companies also have to consider the laws of international markets if they are aiming to introduce their smart packaging solutions to overseas companies.

*Cole:* For some types of smart packaging there aren't any international standards. We don't have any official guidelines for smart labelling solutions for track and trace, for example; however, as the technology is relatively new, there is work underway to develop those standards. We need a large-scale demonstration of smart packaging to develop case studies that show its value.

*Tallant:* As an industry, we embrace regulations because they provide the backbone for product protection. Despite being a new concept, smart packaging should not impact compliance or the ability to meet regulations. But a major issue for smart packaging manufacturers is the fact that the manufacturing process is subject to validation, meaning that all processes are documented and consistent. Modifying packaging into smart packaging typically requires re-validation of the line and the process – something manufacturers try to limit. And so that's a barrier to adoption for most smart packaging technologies.

*Roemers:* Although the industry already has guidelines like GAMP5 (a guideline published by the International Society for Pharmaceutical Engineering) to achieve compliance with computerized systems, the risk of human error and cost pressures are always present, which compromise the integrity of the supply chain and the quality of medicines. The supply chain is also vulnerable to temperature variation (which has the potential to result in spoiled products) and counterfeiting due to its long and fragmented nature.

*How have patients and healthcare practitioners reacted to currently available smart solutions?*

*Cole:* Some smart packaging solutions are in use in phase I clinical trials and are showing benefits. However, in the commercial supply of medicines, we don't see much in the way of these products penetrating the market. I would assume that healthcare professionals would be positive about innovations that improve adherence; however, from discussions, they may struggle to work with innovations that feed information back to them. For example, if a smart pill pack indicates that a patient is not taking their medicine and this information is relayed to the doctor, does the doctor have a duty of care to act on this information? Also, do clinicians have time to be monitoring

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patients that are using novel technologies? This area requires research and large-scale demonstration projects.

*Tallant:* Today, people have an increasing expectation for connected “everything” – and it also applies to prescription medications, where practitioners and patients are looking for smarter packaging. As this area of industry continues to grow, there will be more opportunities for smartphone engagement and information dissemination.

*Smith:* Steve is right; patients and healthcare practitioners alike rely on smart and connected devices every day. Who doesn’t own a smartphone? And we’ve seen a proliferation of associated smart devices – you can now perform an ECG on your wristwatch... The idea that a package can monitor and help with adherence is an extension of what patients already use – and I think it will be warmly welcomed.

### *What will encourage more companies to adopt smart packaging?*

*Smith:* The fact of the matter is that a healthier patient is less likely to need costly hospitalization. We all understand that adherence is a major contributing factor to a patient’s health, so when presented with options that can help improve patient outcomes, shouldn’t the industry want to embrace them wholeheartedly?

At this point, however, prescription insurance providers will not cover any incremental cost that comes with the use of smart packaging. As a result, drug manufacturers are reluctant to use this technology in commercial Rx products, particularly in the US.

*Tallant:* The adoption of smart packaging options has been slow, but there is definitely a growing interest. A greater awareness of what they can offer in terms of leveraging serialization is now needed. As more companies begin to realize the benefits of using 2D barcodes to create connected smart packaging features, we should begin to see the transformation of pharmaceutical supply chains.

*Cole:* Pharma is engaging with simple smart packaging concepts, such as printed codes, due to the legal requirements to serialize in Europe and in the US. But pharma is also very positive about adopting more complex smart packaging concepts, including RFID, NFC or flexible electronics. Questions that arise include: how will this fit in with our current manufacturing lines? What value do such innovations deliver? Pilot and industrial scale manufacture and demonstration projects, the type that CPI has the capability to be involved in, will be crucial in showing the value of smart products and will help in the development of manufacturing processes that could be adopted by pharma and their suppliers.

*Stein:* It’s understandable that healthcare companies are adopting smart packaging at different rates. Enabling technology solutions in healthcare is very different than most other industries because human lives are involved. With that said, we’re working with many pharma companies who are eager to embrace what smart packaging has to offer; from our point of view there is a strong rate of adoption, which is constantly growing.

### *What does the future hold?*

*Cole:* As the sensors and batteries we use become smaller and more integrated, smart packaging will become seamless and embedded in pill packs, bottles, and other types of packaging. I hope to see them become the norm, helping to support patients to take their medications and adding value to the digital ecosystem.

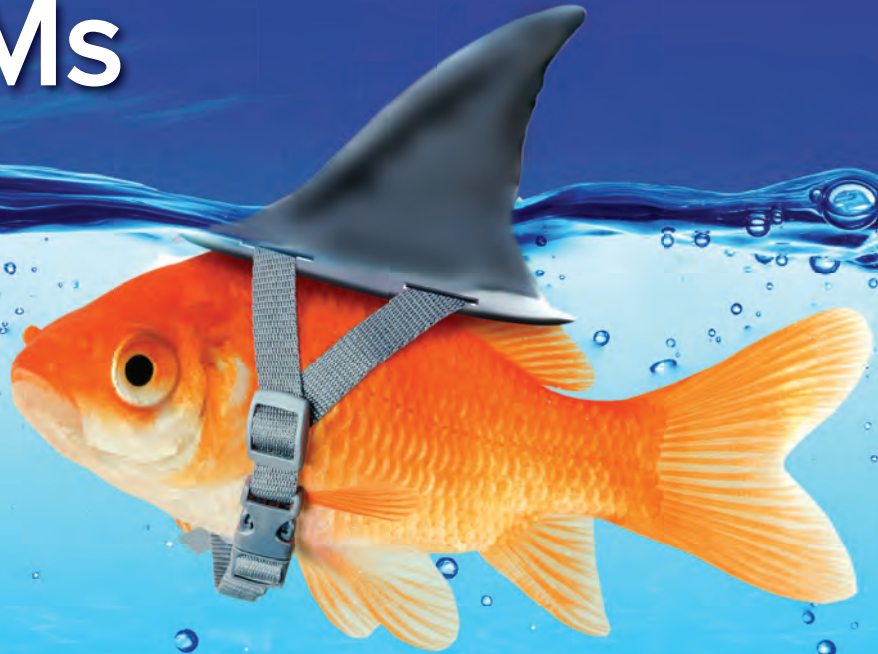
*Tallant:* I believe that ideal pharma packaging already exists within the serialized regulatory framework. Adding the ability to transform a package into a smart package, by leveraging the existing serialized barcode, makes this possible today. As more and more companies take advantage of this possibility, adoption will rise, and patients and practitioners will take advantage of what more digitized packaging has to offer.

*Roemers:* As more businesses begin to embrace what smart packaging solutions have to offer, we should begin to see a future where hassle-free operations can be realized. The industry is already trialling a variety of digital solutions and slowly beginning to see the value in them. When a company can monitor every shipment box it owns because of automatic data collection through gateways or smartphones, or eliminate human interaction in data collection (resulting in improved accuracy), they are bound to see how attractive smart packaging can be.

*Stein:* When people look at smart packaging, they may incorrectly assume that all types of smart packaging are the same, but they are not. Think of something as simple as a mobile phone; the capabilities of a flip phone for sending emails and helping its user navigate through a city pale in comparison to a smartphone’s – if they are able to do so at all.

The key to making a device really powerful is the backend data analysis engine which powers any smart packaging solution. Looking forward, new iterations of products and software will be released to continuously enhance the overall experience for patients and healthcare practitioners – which will continue to drive powerful evidence-backed results.

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# Small Molecules, Sizable Market Opportunities

Business

The small molecule drug development pipeline is booming! And with shrinking clinical trial cohorts (especially in oncology and orphan indications), smaller and virtual companies are now able to take candidates further than ever before.

*By Stephan Haitz*

Often, it feels that statements such as, “Although small molecules remain the largest portion of the pharma industry, they are on the decline, with large molecules and advanced medicines set to dominate in the coming years” are the prevailing narrative in the industry. But does it stand up to scrutiny?

Looking at market data, the number of small molecules being developed as drug candidates has increased over the past five years (see Table 1 on page 20). The growing number of preclinical candidates coming into existence has boosted pipelines, and there are more phase I trials taking place than ever before, with more than 7,500 launched or entering development over the past five years. In addition, 520 potential drug compounds advanced from one clinical development phase to the next in 2018, suggesting that the industry is continuing to invest in small molecule drugs – particularly in areas such as oncology and orphan diseases.

Big opportunities for small companies  
There is a growing trend for smaller and virtual companies to push projects further through the development pipeline than



they typically would have in the past. For example, 65 percent of clinical pipeline projects are now sponsored by small companies (see Figure 1 on page 20). Previously, the high costs of clinical trials meant that only the larger companies had the resources to support late-stage development, including final drug product approval. Now, with the clinical pipeline continuing to focus on smaller patient

clinical trial cohorts requiring fewer resources, smaller and virtual companies have the resources to support late-phase trials. They may, in some cases, even be able to commercialize these assets.

Another positive sign of the health of the small molecule sector is the amount of venture capital funding available, which includes investment for the early-stage life science companies that

are developing the majority of new chemical entities (NCEs). In fact, in 2018, experts estimated that more than \$60 billion was raised in IPO funding, follow-on funding, private investment in public equity, as well as venture capital and funding from other sources. Of this, a record \$20 billion was in the form of venture capital funding for start-ups and early-stage companies.


The large and growing small molecule API market (an estimated value of \$25-35 billion in 2018 ) is also characterized by increased outsourcing, particularly by small and virtual pharmaceutical companies; despite the increased draw of biologics and cell-based therapies, the small molecule market remains an attractive business area for contract development and manufacturing organizations (CDMOs).

*“The small molecule market remains an attractive business area for contract development and manufacturing organizations.”*

With the pharmaceutical industry currently focusing more on the quality of the drug product rather than on cost – as it had in the years since the turn of the century – drug companies are

now returning to Western CDMOs for the manufacture of drug candidates and drug substances. These trends, as well as the industry’s growing and fast-moving clinical pipeline and the highest FDA approval rate since the 1990s, are the reasons for the considerable optimism now found throughout the drug development sector.

Orphan drugs and the oncology scene  
A total of 42 NCEs were approved in 2018, and 38 in 2019 – a considerable increase on the average of 25-35 NCE annual approvals seen in recent years. And looking at the broader commercial market (beyond approvals), consumption data for all small molecule prescription drugs in seven major markets (US, UK, France, Germany, Spain, Italy and Japan) shows a total volume of 3,500



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	2014	2015	2016	2017	2018	2019	CAGR (14-19)
Preclinical	2,273	2,692	3,016	3,206	3,193	3,624	9.8%
Phase I Clinical Trial	633	698	797	836	891	964	8.8%
Phase II Clinical Trial	730	782	814	849	912	922	4.8%
Phase III Clinical Trial	195	211	260	282	270	296	8.7%
Total Clinical Pipeline	1,558	1,691	1,871	1,967	2,073	2,182	7.0%
Pre-Reg/Reg	57	49	55	66	75	66	3.0%
Launched	1,439	1,479	1,510	1,531	1,562	1,601	2.2%
Total Commercial Pipeline	1,496	1,528	1,565	1,597	1,637	1,667	2.2%
Total	5,327	5,911	6,452	6,770	6,903	7,473	7.0%

Table 1: Small molecule New Chemical Entities (NCEs) pipeline 2014-2019 (data from Cambrex/Citeline).

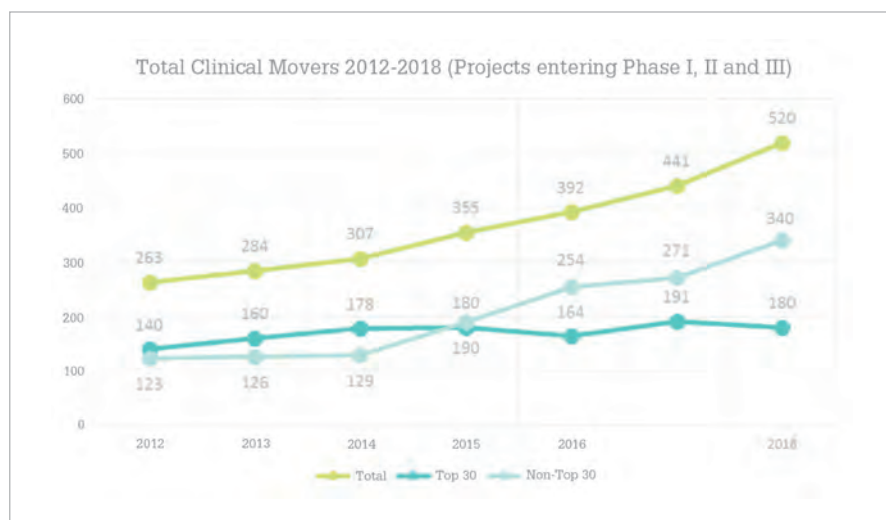


Figure 1: Total small molecule clinical movers 2012-2018 (data from Cambrex/Citeline).

metric tons with an annual growth of around 100-200 additional metric tons of API each year. This includes continued growth of the large, 100-ton-plus, high-prevalence-disease sector, as well as of the 10-20 ton range representing the more-targeted therapies, including orphan drugs.

Another recent trend is increasing investments by CDMOs in facilities for the manufacture of highly potent APIs (HPAPIs). The number of

small molecule cancer treatments in development is a good indicator of the robustness of the HPAPI sector as a whole (most HPAPIs are being developed for the oncology sector). Overall, the small molecule oncology pipeline is growing well, now accounting for 38 percent of small molecule drug candidates in preclinical development, 35 percent of clinical-stage small molecules, and one third of recent FDA approvals. Revenue

*“Small molecule drug development is not declining – on the contrary!”*

and volume data for the 252 oncology drugs on the market or in registration in 2019 shows a market value of almost \$53 billion and a volume of 920 tons – significant compared with the typical commercial API volumes of around five tons per molecule.

CDMOs have reacted to these market trends by building in capacity on the assumption that all oncology drugs are highly potent with Operational Exposure Limits (OELs) in the 1-10 µg/m<sup>3</sup> range. This is, therefore, an area of considerable interest for CDMOs given their expertise in handling such high-potency products and the current preference of the pharmaceutical industry for using Western suppliers.

In summary, small molecule drug development and manufacturing is not declining – on the contrary! We see more drugs at the clinical and preclinical stage than ever before, with record numbers of patients being prescribed small molecule drugs, for a wider range of conditions. Highly-potent products, especially in oncology and orphan indications, are particularly strong today. This is good news for the CDMO sector, which is benefiting from the demand for fully integrated services and experience with HPAPIs, and for small and virtual companies, which are able to take therapies further than ever before.

*Stephan Haitz is President, CDMO Sales & Marketing at Cambrex*



## Designed With You in Mind

The best machinery can only be made with the input of the people who use it everyday

By Michael Benjamin

Before joining Diosna, I spent around a decade in various pharma manufacturers and CDMOs in Germany. As a pharmaceutical engineer, I'd always been fascinated with equipment and I really hoped that, one day, I could use my experience to help optimize those systems. When you are operating equipment on a day to day basis, shortcomings in the design quickly become apparent. I came to Diosna four years ago with a vision: simplifying the lives of people in the pharmaceutical industry.

The modular trend for CDMOs  
Current trends across the pharmaceutical industry are moving towards specialized, highly potent drugs and smaller batch sizes. And that means pharmaceutical manufacturing equipment must be flexible, versatile, and modular. Many pharma companies choose to outsource some of their manufacturing operations so that they can primarily focus in-house resources on scientific research and marketing. And when medicines are made in smaller batches, it's often advantageous to let a CDMO do the manufacturing work. For CDMOs, flexibility is even more crucial. CDMOs work with a variety of clients and need access to diverse technologies – from traditional to cutting edge – to suit client demands. At the moment, modular equipment is a key trend, with a number of CDMOs requesting these types of machines.

The MINILAB RC and the MIDILAB RC are two examples of modular, plug and play machines that are particularly popular with CDMO customers. The MINILAB RC is

designed for process development and is able to combine the main pharmaceutical technologies – drying, granulation, and tablet coating processes – using modules. Meanwhile, the MIDILAB RC combines high shear mixing, fluidized bed and tablet coating processes in one system. Where these capabilities might otherwise require four or five rooms, both of our systems are simple benchtop devices operated by a touchscreen. All you need is compressed air and a power supply – and then, wherever you are, you can directly start manufacturing. The exchanging of modules is done without any tools, and takes less than five minutes.

Within the modules is a range of bed sizes suitable for 40 g to 16 kg. With this range, you can operate many different batch sizes – and, in my view, this is exactly the type of technology that CDMOs need; the range gives them flexibility. Scale up is always a challenging process, and so being able to scale up using just one machine makes a significant difference.

### Meeting real needs

Traditional pharma companies also value flexibility and modular machines – and the two systems mentioned above have been welcomed by pharma manufacturers as well. Aside from flexibility and modularity, however, there are other features that are important in good equipment:

- Hygienic design. The ability to easily and thoroughly clean the machine is key to reducing the risk of contamination. Ideally, cleaning should be automated.
- Process Analytical Technology (PAT). The FDA has encouraged the industry to use PAT to improve processes and efficiency. Optionally our machines incorporate PAT technologies, such as NIR spectroscopy for in-line humidity testing.
- Ease of operation. Inclusion of



features like adjustable screens that enable operators to keep track of the process, while having the controls immediately at hand, make the lives of users much easier.

- Assembly. If the size of the machine permits it, there shouldn't be any tools that require GMP approval for assembly or disassembly.

In our process lab, customers are given the opportunity to test our machines with their pharmaceutical products – with the guidance of our expert pharmaceutical engineers and operators. This not only provides practical training for the customer in terms of how the machine works, but is also a valuable opportunity for us to get feedback from the customer, which can be used to further improve our systems. We discuss what could be changed and what we could improve just to fit the demands of the customer. In this way, equipment can constantly evolve and advance.

Diosna will be exhibiting their range of machines, including the MINILAB RC and MIDILAB RC, at Interpack in Dusseldorf, 7–13 May 2020.

*Michael Benjamin has more than 10 years of experience working in solid pharmaceutical development across a number of different pharmaceutical manufacturers, including one of the biggest CDMOs in Germany. He is currently Head of Pharmaceutical Laboratory at Diosna.*



# Exploring Hot-Melt Extrusion

## Inside the Medicine Machine

When it comes to developing a viable formulation for an API with poor solubility and poor bioavailability, manufacturers should look to hot-melt extrusion (HME) – a well-established process that is easy to scale up with the right mathematical models

*By Sampada Upadhye*

First developed for polymer processing in the plastics industry in the 1930s, hot-melt extrusion (HME) is a well-established and flexible technology in the pharma industry. HME facilitates the formulation of low-solubility, low-permeability drugs into a number of patient-friendly dose forms, including tablets, capsules or free-flowing granules.

HME uses heat and pressure to melt a polymer before it is forced at constant pressure through an orifice (see sidebar: “How HME Works”). The resulting “extrudate” is then further processed into products that display uniform API particle distribution and density. HME has become widely used in drug product development, because of the added flexibility it offers; by selecting suitable polymeric matrix excipients, formulators can create products that achieve higher bioavailability (than traditional formulations) as well as targeted delivery into the upper regions of the intestine, when drugs have poor solubility and/or poor permeability.

Poorly-soluble APIs are a key challenge for the development of solid dosage forms. The more efficiently the active ingredient can be released from a specific delivery system into the bloodstream, the better its bioavailability. It is estimated that up to 90 percent of all newly-synthesized APIs are poorly soluble and almost half of drug development project failures are due to a lack of API solubility and the resulting poor drug bioavailability and/or



variable pharmacological behavior (1).

Dissolution rate is also important for the absorption of orally ingested substances; a drug is practically unavailable if the dissolution time of an active is longer than its gastrointestinal transit time. The dissolution rate itself is not only determined by the geometry and the surface of the particles, but also by the concentration difference between the saturation concentration and the actual solution concentration. This difference can be very small for poorly soluble compounds, so the surface and the geometry of the particles become the most relevant parameters for the dissolution process.

For APIs exhibiting solubility-limited absorption, solid dispersions and solutions can be obtained in a number of ways using solution processes in which materials are

dissolved in a suitable solvent and then converted into amorphous form using spray drying, freeze drying, casting techniques, or by using melt processes. There are several major processing advantages of HME:

- HME is a solvent-less process
- The HME process is independent of the compressibility characteristics of the starting material
- HME is a continuous, well-controlled process based on co-rotating twin screw technology that offers good blending characteristics, resulting in an API that is homogeneously dispersed or dissolved in the carrier matrix
- The HME process is unaffected by any crystalline modifications

## How HME Works

The extrusion process combines conveying, melting, blending, kneading, and degassing into a continuous process, and the various substances involved are continuously added into the processing section or “barrel” of the extruder in a precisely controlled manner. Co-rotating screw shafts regulate material transportation and mixing, and determine the residence time in the various zones. Different temperature profiles can be applied in each zone to meet the processing needs of the polymer and the API, while air or other gases are removed from the molten mass using a vacuum unit to guarantee a bubble-free discharge of molten extrudate through a nozzle at the end of the processing section. A solid product is formed upon cooling of the molten extrudate, and this can be used in downstream processes to develop the desired solid oral dosage form.

Twin-screw extruders, which are predominantly based on segmented screws, can be configured in various ways to meet different conveying, kneading and

blending requirements. The important parameters of the screw elements are the element pitch and the number of flights, as well as the outer and inner diameter of the screws. Pitch affects the residence time of the material in the processing unit, while the material flow rate depends on the number of flights in the screw elements. The torque transferred to the screw determines the material throughput.

Mixing and compensation of concentration differences is achieved by the mixing elements of the equipment, such as kneading blocks: staggered kneading discs hinder the flow of the extrusion mass along the main conveying direction, while refracted and redistributed material flow results in a distributive mixing effect. In addition, the use of reverse-conveying screw elements improves intermixing. Thus, the ability to arrange the extruder's screw elements in almost any combination allows the extruder to be adapted for almost any extrusion task.

For the extrusion of APIs, barrel temperature, screw speed and feed rate are the most important process

parameters. Low screw speeds result in a long residence time of the material in the extruder, potentially leading to an increase in degradation and impurities, while high screw rotation speeds may cause incomplete mixing and physical instability resulting in recrystallization of an amorphous API.

The shaping of the molten mass occurs when passing under pressure through a die with a narrowed cross-section, and the die flow channel must be aerodynamically designed to allow proper melt flow to be achieved. In addition, the elasticity of the polymer melt and its cooling rate after passing through the die are important – at this stage, the pressure and temperature should be constant to obtain a uniform product.

Solid carriers, excipients and APIs are dosed either individually or are combined in a precisely controlled mixture for dosing, with gravimetric dosing systems being preferred over volumetric dosing systems in pharmaceutical applications. Liquid or gaseous components may be introduced directly into the melt through side feeding devices.

of the API because it is based on amorphous solid dispersion in a carrier matrix that provides flexibility in downstream processing and the ability to produce a range of formulation types

- HME allows the introduction of taste-masking techniques.

For the HME approach to be successful, the time in which the systems can be cooled down to temperatures below the glass transition temperature ( $T_g$ ) is of great importance – a factor that also affects aggregation and crystallization of the API. Drug formulations with targeted release kinetics are achieved by a molecular dispersion of the active substance in the carrier matrix. The choice of process parameters and the screw design determine the quality of the extrudate; small amounts of active ingredient are sufficient to evaluate the suitability of an HME process with regard to processability

and quality characteristics of the extrudate. A systematic approach to HME based on an understanding of the interplay between process and product enables the development of stable amorphous solid dispersions, and the rapid scale-up of clinical manufacturing.

### Points to remember

To develop suitable formulations, it is beneficial to keep the extrusion formulation process as simple as possible through the choice of a suitable polymer. The use of a plasticizer for improved processing should only be used if necessary, and a solubilizer will be required for improved solubility and prevention of recrystallization when in the presence of gastric and intestinal fluids.

Selection criteria for the polymeric carrier to be used in the HME process include its interaction with the drug; the potential for supersaturation; and the solid-state solubility of the drug in the carrier. Important polymer characteristics include the design of the

manufacturing process, the solubility of the polymer in water and organic solvents, its molecular weight and its glass transition temperature. Ideally, the polymer matrix acts as a solid solvent and the drug is molecularly dissolved. To achieve this, the polymer should have good thermoplastic behavior (deformability is essential); thermal stability ( $T_g$  from 50 to 200°C); low hygroscopicity to prevent crystallization; and no toxicity (so that it may be used in large amounts).

A number of analytical techniques are used to control the quality of the extrudate, including optical microscopy to determine sample surface morphology and the presence of crystalline particles; scanning electron microscopy (SEM) for higher-resolution imaging; and atomic force microscopy (AFM) to provide three-dimensional images. Differential scanning calorimetry (DSC), X-ray diffraction crystallography (XRD), solid-state nuclear magnetic resonance (ss-NMR), and IR and Raman



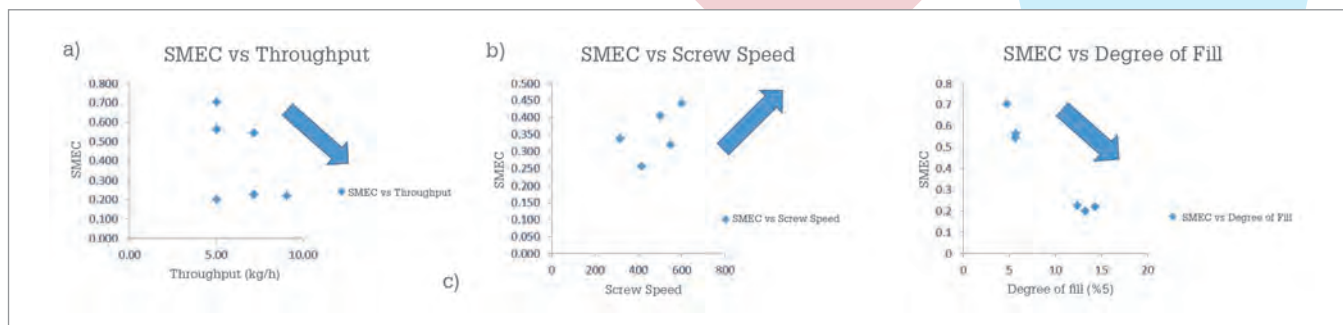


Figure 1. Trends in the relationship between SMEC and a) throughput b) screw speed c) degree of fill when run on a 27-mm TSE.

spectroscopy can also be used to analyze the quality of the API/polymer extrudate.

### The QbD approach

HME enables product development driven by Quality-by-Design (QbD). Parameters, including the degree of dispersion, level of impurities, extent of dissolution, stability and morphology, can be optimized through the application of an extrusion process in which characteristics such as residence time and shear stress are controlled via a number of input variables. These include feed rate, temperature, screw design, screw speed and the physical properties of the materials.

We have developed a mathematical approach to the scale-up of HME from laboratory-scale to production-scale for the manufacturing of a drug for a phase II program. The approach (OptiMelt Plug & Play) predicts HME process-independent parameters. Specific mechanical energy consumption (SMEC) is the critical process response in the scale-up of the HME process. It is defined as the energy supplied to the material by the extruder motor and is dependent on the screw configuration and speed.

SMEC can be used to predict critical process parameters (CPPs), such as screw speed and feed rate, and degree of barrel fill to ensure successful scale-up.

*Equation 1.  $n$  = screw speed (rpm),  $\tau$  = Torque [Nm],  $m$  = throughput [kg/h]*

Converting the SMEC from the laboratory-scale extruder to larger-scale extruders via the calculation model identifies

the new process parameters. The predictive model also provides an estimate of product quality and helps ensure the set quality target product profile (QTPP) is met for both small- and large-scale batch sizes.

In the below example, the application of the SMEC calculation model from laboratory-scale studies aided in the creation of a design space to produce a stable amorphous indomethacin extrudate during the scale-up process (see Figure 1).

The CPPs (screw speed and feed rate) can be optimized to achieve the desired scale-independent responses, and maintained within the specified design space for efficient manufacturing. Scale-independent process response, such as SMEC, is ideal for associating the quality to the process. Changes in equipment size, brand, and/or location require the determination of the impact that these factors may have on the CQAs of the process inputs, if they are to ensure a successful tech transfer of an HME process.

At the end of laboratory-scale development, not only could the clinical trial supply be manufactured, but it is also possible to make a sound risk assessment that supports further scale-up by using a reasonable amount of API.

An integrated end-to-end HME process platform provides the capability to formulate, develop and commercialize differentiated final dosage forms. It enables a holistic approach to bioavailability enhancement by broadly addressing multiple bioavailability factors, including optimization of product efficacy, safety

and release properties. Beginning with initial API and preformulation studies, the required formulations can be developed through the application of a range of screening technologies and analyses.

### Formulation flexibility

Although twin-screw hot-melt extrusion has been more popularly used for manufacturing amorphous solid dispersions, twin screw extruders are versatile pieces of equipment. They are also used for continuous manufacturing of immediate release and controlled release products of crystalline API. Based on the target product profile of API, various extrusion granulation techniques, such as wet, dry and melt granulation approaches, can be employed to yield appropriate immediate release and controlled release product.

In summary, bioavailability enhancement and dose form flexibility can both be achieved through the application of HME technology. Moreover, the wide range of dose functionality achievable allows immediate and controlled-release formulations to deliver more active drug, when and where it is needed in the body.

*Sampada Upadhye is Global Study Director, Hot Melt Extrusion Technology, at Catalent*

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## *Diosna* CCS Granulation Line

The Diosna Closed Combined System (CCS) offers the principal elements of a state-of-the-art solids production plant – the high-shear granulator and fluid bed dryer (top-, bottom-, and tangential-spray) – all in one system.

The CCS is 12-bar shock-resistant, and is able to accommodate sizes from 10 up to 1600 liters.

The system provides efficiency with automated processes, short set-up times and easy material transfer for wet granulation, drying and final sieving.

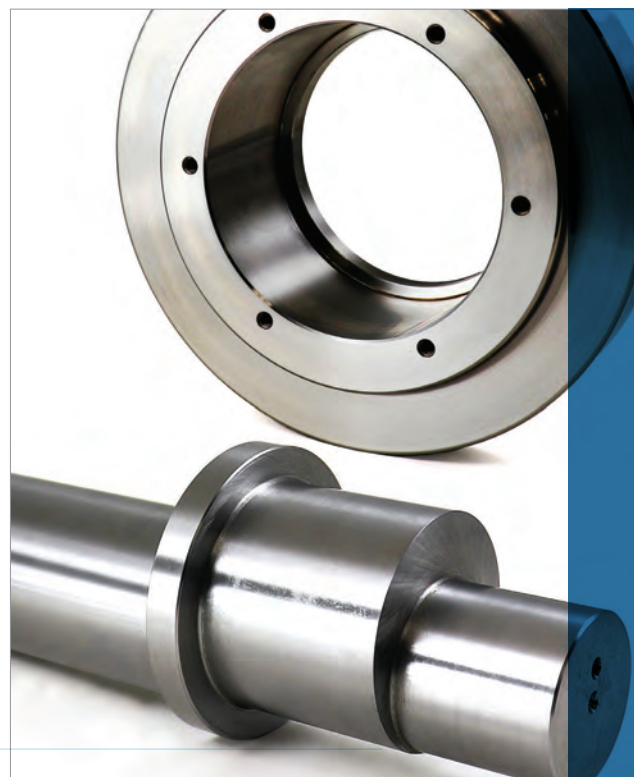
The integrated PAT tools allow in-line humidity testing, particle size measurement and more.

CONTACT: [info@diosna.de](mailto:info@diosna.de)  
WEB: [www.diosna.com](http://www.diosna.com)

## *Elizabeth Companies* Tablet Press Replacement Parts

Elizabeth Companies offers the industry's largest selection of high precision tablet press replacement parts to fit over 140 tablet presses. Using the highest grade steels and alloys available, they manufacture replacement parts to exacting tolerances utilizing the latest in manufacturing technologies. If in the rare case they do not manufacture the part you need, they can duplicate your OEM part with unparalleled accuracy and even upgrade material selections to better suit your product.

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# One Vision, One Culture, One Team

Sitting Down With...  
Mike McMullen, President  
and CEO, Agilent Technologies,  
Santa Clara, California, USA



As a leader of a company that must innovate to succeed, how do you maintain momentum?

Innovation is in our DNA at Agilent – and that philosophy must extend beyond the R&D community. Yes, we must develop products at the cutting edge for our customers, but we must also be innovative when it comes to how we work with our customers – and how we run internal operations. It's easy to talk about these things – but do you actually run the business this way?

When I first took on this role in 2015, I discussed profitability goals with the investment community, as you might expect. “Well, Mike,” they said. “Why not just cut your R&D budget in half, and you'll reach your goals much faster...”

“That would destroy who we are,” I replied. “We are an innovation driven company.” And that's why we are willing to invest such a high percentage of our revenue into R&D – over \$1 billion in the next three years. We're also the only company in our space with a long-term basic research effort – Agilent Labs, staffed with world-class scientists developing the technologies of the future.

What trends are driving innovation within Agilent?

Consider your smartphone – you're probably less interested in the underlying technology than the experience it enables. When it comes to analytical technology, while yesteryear's users may have built their own instrumentation, today's users simply want to ensure that it meets their workflow needs. Our technology is trending towards smaller, faster, easier to use, and better integrated – back to my analogy: everyone now has a far more powerful computer in their pocket than the one I had on my desk when I started at Hewlett-Packard...

At the beginning of your career, did you ever envisage becoming the CEO of an analytical giant?

I can't remember ever looking that far ahead! And, in fact, when I dispense career

advice, my first pearl is: “Don't over manage your career – because you never really know where it will take you.” My second piece of advice: “Always follow the experience and accept opportunities to learn.”

When I finished my MBA at The Wharton School at the University of Pennsylvania in the 1980s, the next step should have been Wall Street. And though I had job offers on the table from investment banks, I recognized that I really didn't want to enter that world.

I wanted to work for a company with a mission – a company that developed and created a tangible product. At Hewlett-Packard, I knew that my ability to progress was only linked to my willingness to develop myself and take a few personal risks. I entered the company as a financial analyst, so perhaps dreamed of becoming the Chief Financial Officer one day... But as I moved through my career, I learned that I had inherent leadership qualities.

Over time, I built up a track record of growing businesses and turning businesses around. When we created the new Agilent in 2015, I was asked to become the third CEO. Notably, my predecessors were both R&D engineers. And that links to another piece of advice: “Don't allow people to put you in a box or tell you what you can't do.”

What's your best moment as CEO (so far)?

Easy: when we received the results of one of our leadership surveys – about three years into our journey. Every six months, we ask all 16,000 Agilent employees how we're doing. We recruit an external consultancy team to analyze the results and compare us with the best out there. Our scores for employee engagement had grown significantly over that relatively short period; apparently, we were “best in class.” It's great to make investors happy with rising stock prices, and to see customers reacting more positively to their experience with us. But I am most proud and satisfied by how our employees

feel about working at Agilent – because that's really how we've achieved our other goals. There's plenty of information out there pointing to the fact that companies with highly engaged workforces do well. And it was great to have proof that I wasn't just being a delusional CEO...

A great deal of attention is on biopharmaceuticals and advanced medicines, but small molecule drugs are still highly important. What trends do you see – and how is Agilent innovating in this area?

First of all, the pharmaceutical market is the largest market for Agilent, at over 30 percent of our revenue. We have been working hard to become a broader supplier to customers in that market. Recently, I was with the investment community in London and everyone wanted to talk about biopharma, which is very exciting and has high growth rates – and, of course, Agilent has solutions in that space. But I'm always very quick to remind people that small molecule pharma is not going away – and it is being driven by the need to lower costs across the world. And that means the industry needs new tools that allow them to do more with less, or to be more efficient in QA/QC, for example.

But supplying the right tools is only one part of the solution. My fundamental business strategy for Agilent was not only to help our customers do great science, but also to help them with the operations and economics of the lab. And so, in addition to easier to use, digitally-integrated solutions with smaller footprints, such as the Ultivo triple quadrupole LC/MS system, we've got a whole series of new capabilities for laboratory managers; for example, the potential to monitor instrument utilization and peak run times, to provide troubled asset reports, and so on. Rather than supplying a pinpoint product to an analytical lab, we look at the whole ecosystem – and consider how we can not only integrate into it but also add real value.



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