NOVEMBER 2020 # 08

the Small Molecule Manufacturer®

A Highly Potent Challenge

Experts examine the best practices for safely handling HPAPIs

EXPERIENCE THE DIFFERENCE

THE ELIZABETH DIFFERENCE.

Compression Tooling | Tablet Presses | Turrets | Replacement Parts | Field Services & Training | Tablet Press & Turret Repairs | Blister Packaging Tooling & Feeders

We understand that your products are trusted by consumers each and every day. Consistent quality of your solid dose products is expected and non-negotiable. Your products depend upon the integrity of your equipment and tooling. For over 65 years, Elizabeth Companies have put a personal guarantee on customer satisfaction and takes pride in delivering innovative solutions. We promise our customers an unequaled level of customer service, product performance, prompt and courteous communication, and trust. Experience the difference, THE ELIZABETH DIFFERENCE.

Elizabeth

ELIZ.COM | 412-751-3000

@ELIZCOMPANIES

Fancy a Game of Ping-Pong?

When following COVID-19 research, it's hard to keep your eye on the ball...

Katrina A. Bramstedt recently wrote a provocative article about research during the pandemic (1). "No research team is exempt from the pressures and speed at which COVID-19 research is occurring. And this can increase the risk of honest error as well as misconduct. To date, 33 papers have been identified as unsuitable for public use and either retracted, withdrawn, or noted with concern."

Before we digest those comments, let's not forget to applaud the verve with which the research community and pharma industry have been digging into COVID-19 and its treatment. Never before have we seen so much collaboration or so many new vaccines and treatments advancing through clinical development in such a short time.

But scientific ping-pong has been a key theme throughout the pandemic (and indeed throughout history, albeit at a more leisurely pace), which has ultimately led to confusion. When governments or key political figures cherry pick the science and findings to drive (or suit) their healthcare policies and decisions, the waters become murkier still. Ultimately, public trust in health leaders is being eroded – and that could fuel vaccine hesitancy when we finally get an approval.

At Texere Publishing, we publish a weekly newsletter – the COVID-19 Curator – which pulls the most important science stories together into three categories: understanding, testing, and fighting; sign up (free): https://www.texerenewsletters.com/covid19newsletter. As part of the curation team, I've watched some epic games of table tennis. Hydroxychloroquine is a wonder drug. It doesn't work. It might work. It doesn't work. COVID-19 produces long-lasting antibodies. It doesn't produce long-lasting antibodies...

And now it seems a new small molecule contender is entering the game. When remdesivir received conditional marketing approval in some regions, it received a great deal of global attention. However, the WHO's Solidarity trial, which studied remdesivir and three other drug regimens in over 11,000 hospitalized patients, concluded that none of the treatments substantially affected mortality or reduced the need for ventilation (2).

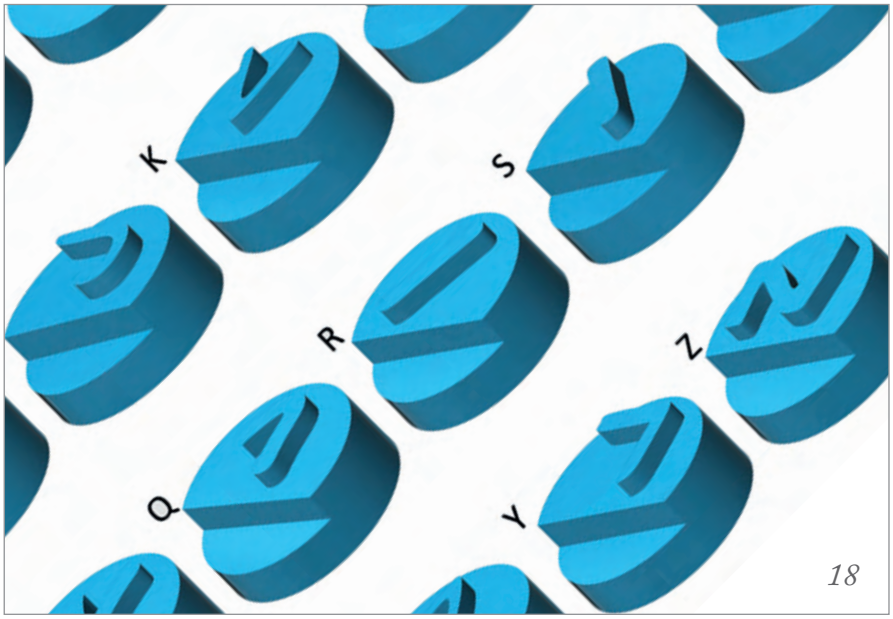
Is remdesivir a dead end – it depends which scientist you ask. Despite the results of the WHO's trial, the FDA has approved remdesivir under the brand name Veklury for treating hospitalized COVID-19 patients. One thing's for sure, fans of ping pong will not be disappointed as COVID-19 science moves forward (and then back again).

Stephanie Sutton
Editor

References

1. *K Bramstedt, "The carnage of substandard research during the COVID-19 pandemic: a call for quality," Journal of Medical Ethics (2020).*
2. *WHO, "Solidarity Therapeutics Trial produces conclusive evidence on the effectiveness of repurposed drugs for COVID-19 in record time," (2020). Available at https://bit.ly/349d1zw.*

Contents



the Small Molecule Manufacturer

ISSUE 08 - NOVEMBER 2020

Change of address info@themedicinemaker.com
Hayley Atiz, The Small Molecule Manufacturer, Texere Publishing Limited, Booths Park 1, Chelford Road, Knutsford, Cheshire, WA16 8GS, UK

General enquiries
www.texerepublishing.com | info@themedicinemaker.com
+44 (0) 1565 745 200 | sales@texerepublishing.com

Distribution: The Small Molecule Manufacturer (ISSN 2633-0482), is published monthly by Texere Publishing Limited, Booths Park 1, Chelford Road, Knutsford, Cheshire, WA16 8GS, UK. Single copy sales £15 (plus postage, cost available on request info@themedicinemaker.com). Non-qualified annual subscription cost is £110 plus postage

Upfront

Research
Trends
Innovation

The Gut Response

Shedding light on the microbiome's interaction with oral medicines

What happens when first-line treatments fail? For patients living with prostate cancer, androgen deprivation therapy (ADT) is often the first approach. The treatment lowers the levels of male hormones in the body, starving the cancer – but it doesn't work for everyone and many researchers have sought to find out why.

Jeremy Burton, Research Chair in Human Microbiome and Probiotics at Lawson Health Research Institute and an Associate Professor at Western University, believes the microbiome could hold answers. In a new study, Burton and his colleagues explain how our microbiota interacts with abiraterone acetate (AA) – an oral steroidal progesterone derivative used in patients resistant to traditional treatment options (1).

"Many medicines have never been assessed for their potential to be modified by our gut bacteria," says Burton. "We were interested in AA because it is administered orally to patients and most of the medication is not absorbed and stays in the intestinal tract, it also demonstrates less resistance and higher efficacy rates compared with ADTs, which are administered systemically."

The team monitored the microbiota of 68 men either taking AA or not, using their stool samples to determine how different bacterial species responded to the drug. "We found that AA promoted the anti-cancer-associated bacterium Akkermansia muciniphila," Burton says. He went on to add that A. muciniphila was the microbe that gained the most growth advantage when exposed to the drug – indicating that it was the chief regulator of the microbial changes they observed.

"A. muciniphila was also associated with an increase in bacterial metabolism genes predicted to be involved in the biosynthesis of vitamin K2. Given that the vitamin can target prostate cancers resistant to ADTs in vitro, these results may help explain the higher-than-expected efficacy of AA," he says.

The team plans to further investigate the influence of AA on A. muciniphila and have already started exploring how other drugs affect the microbiota. "Learning about these interactions will likely lead to a future where microbiome pre-screening is commonplace in personalized medicine," Burton says. "We may be just as likely to undergo a microbiome analysis as we are to receive a test on our own genomic material to determine the inter-compatibility of drugs and treatment outcomes."

Reference

1. *BA Daisley et al, Nat. Commun., 11, 4822 (2020).*

INFOGRAPHIC

Small Molecules in the US

Key facts and figures about the small molecule drug market in North America

Market value in 2019:
US$12.79 billion

Expected value in 2027:
US$26.46 billion

CAGR:
9.8%

BUSINESS IN BRIEF

Powder testing partnership, NASH breakthrough designation, and new CEO appointments. What's new for pharma in business?

- TFF Pharmaceuticals has signed a production and manufacturing agreement with CDMO Irisys LLC for an inhalable lung medication being investigated for the treatment of challenging-to-manage severe lung conditions – including COVID-19. Irisys will be responsible for the initial production and testing of the investigational powder product for inhalation.
- Inventiva has received Breakthrough Therapy designation from the FDA for lanifibranor for the treatment of nonalcoholic steatohepatitis (NASH). It is the first potential NASH therapy to receive this status since January 2015. Lanifibranor is an orally-available small molecule that induces anti-fibrotic, anti-inflammatory and beneficial vascular and metabolic changes by activating all three peroxisome proliferator-activated receptor (PPAR) isoforms. A phase III trial is due to begin in the first half of 2021.
- SPI Pharma has named Scott Thomson as its new CEO. Thomson previously spent 29 years at BASF, holding leadership roles in both North America and Germany, including Senior VP of BASF's Global Pharmaceutical Solutions Business. His most recent position was Senior VP Care Chemicals Division, North America.
- Morningside Pharmaceuticals has appointed Tim Brady as its new CEO. Brady has over 30 years' experience working in pharmaceuticals, including building businesses from the ground up and as a European executive for global life sciences businesses. Brady will replace founder Nik Kotecha, who will step into the role as Chairman of the Board.

Pandemic Protection

Influenza treatment passes COVID-19 trial

Fujifilm Toyama Chemical's anti-influenza drug Avigan (favipiravir) has met its primary endpoint in a phase III trial in Japan for COVID-19, including time to negative conversion of detectable SARS-CoV-2 viral RNA in RT-PCR assays, and alleviating symptoms (body temperature, oxygen saturation, and chest images) (1). The company intends to conduct a detailed analysis of the results and potentially file an Application for Partial Changes in Japan. Avigan has been approved for manufacture and sale in Japan for influenza since 2014, but is only used when there is an outbreak of a novel strain or a re-emerging influenza infection where other antiviral drugs are ineffective.

The drug is currently being tested in COVID-19 trials in other countries, with researchers at the KU Leuven Rega Institute recently reporting that a high dose of the API had a potent effect against SARS-CoV-2 in hamsters (2).

References

1. *Fujifilm, "Anti-influenza drug Avigan Tablet Meets Primary Endpoint in Phase III Clinical Trial in Japan for COVID-19 patients," (2020). Available at https://bit.ly/3nHBrIe.*
2. *SJF Kaptein et al., PNAS (2020)*

Benefits of small molecules:

- Diverse in mechanisms of action
- Physiochemical properties and small size make for effective enzyme inhibitors and allosteric modifiers
- Able to target extracellular proteins or intracellular receptors in the cytosol, nuclei and central nervous system
- Can be developed for wide range of indications

Main therapeutic area segments of the North American small molecule drug market:

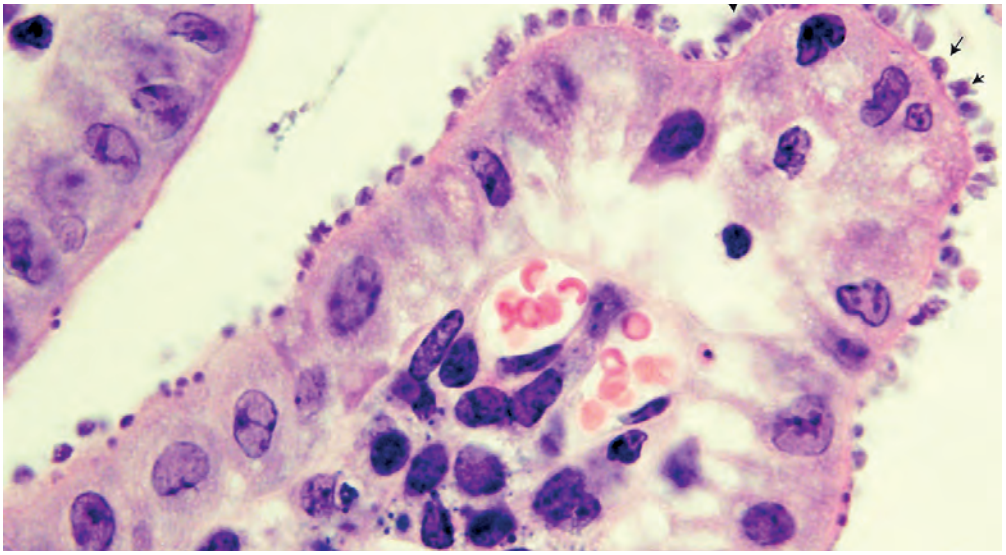
- Oncology
- Central nervous system
- Cardiovascular
- Respiratory
- Orthopedics
- Immunology
- Rare diseases

Rare diseases are expected to register the highest CAGR in the coming years

Source

1. Reportlinker, "North America Small Molecule Drug Delivery Market Forecast to 2027 - COVID-19 Impact and Regional Analysis By Therapeutic Area; Process/ Phase, and Country," (2020).

Credit: The University of Illinois. Sumiti Vinayak.



Putting an End to a Parasitic Problem

Countering a fatal illness with repurposed drugs

Cryptosporidium is responsible for an ongoing healthcare crisis. Found in drinking water, the parasite is responsible for a gastrointestinal illness in children that often causes severe diarrhea and death. Cryptosporidium is a leading cause of diarrheal disease in sub-Saharan Africa, and outbreaks are common in Europe and the US despite the availability of water technologies (1). And though an FDA-approved drug exists for the treatment of the condition, it fails to address the complexities of the disease in malnourished children. Aiming to fill this therapeutic gap, researchers from the University of Illinois are responding to the problem by putting a class of compounds called bicyclic azetidines to the test (1).

Bicyclic azetidines have previously been shown to be effective against the malaria-causing parasite Plasmodium falciparum (1) – a pathogen related to Cryptosporidium. The compounds were found to inhibit the production of transfer RNA in vitro, killing the parasite in the process. And the researchers achieved similar positive results in mice, after administering a daily oral dose over four days.

"This is the first time that the mechanism of action of an anti-Cryptosporidium drug candidate has been confirmed," said the lead author of the study, Sumiti Vinayak, in a statement (2). "It's a good stepping stone to find these compounds that we can feed into the drug-development pipeline. Future research will further evaluate the safety and clinical effectiveness, but the discovery of a new and potent series of compounds with a known target puts us on a promising path forward in this important effort to develop urgently needed treatments."

Reference

1. *S. Vinyak et al., Science Translational Medicine [Online ahead of print] (2020).*
2. *University of Illinois, "Repurposed antimalarial compounds kill diarrheal parasite, study finds" (2020). Available at https://bit.ly/34frCcM.*

Think Small

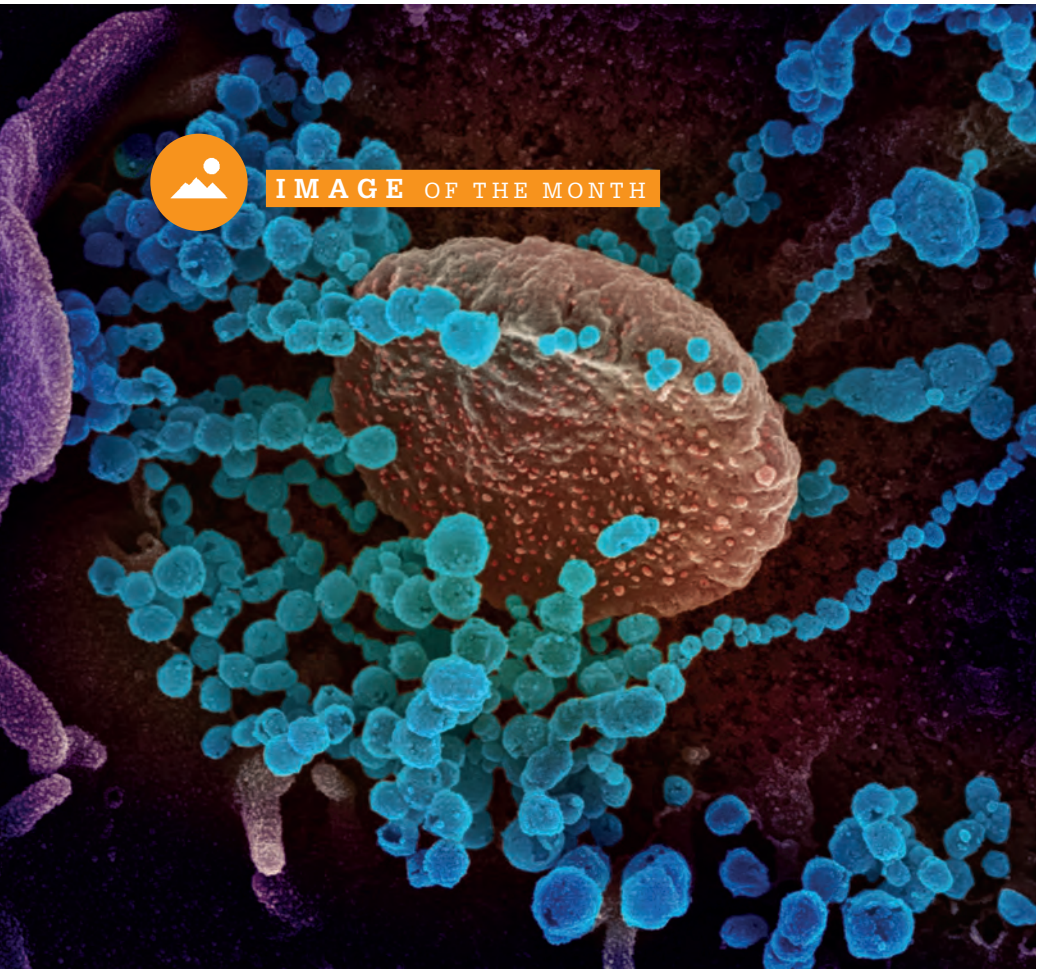
Micro-feeder eases the handling of small quantities of powder

Accuracy and stability are essential when feeding small quantities of powders in a continuous manufacturing process. Agents, such as lubricants, are often only required in small amounts, and the industry is increasingly moving toward highly potent APIs – many of which require feed rates of only a few grams per hour. Conventional feeders struggle to cope with such small quantities, so scientists from the Research Center Pharmaceutical Engineering and the Institute for Process and Particle Engineering at Austria's Graz University of Technology have designed a micro-feeder to tackle the issue (1).

The feeder is based on active volumetric displacement and uses a piston to push powder up out of a cartridge toward the end of a plate. A scraper then places the powder into the process inlet. According to the researchers, the micro-feeder was tested in its ability to feed down to 1 g/hour and "can feed powder with good accuracy and reproducibility, indicating its high potential for continuous process implementation."

Reference

1. *S Sacher et al., Int. J. Pharm., [Online ahead of print] (2020). DOI: 10.1016/j.ijpharm.2020.119969.*



Under the Microscope

Scanning electron microscope image shows SARS-CoV-2 (blue) emerging from the surface of cells cultured in the lab.

Credit: NIAD

Would you like your photo featured in Image of the Month? Send it to maryam.mahdi@texerepublishing.com

QUOTE of the month

"The COVID-19 crisis has shone a light on a long-standing issue: the pharmaceutical supply chain is increasingly consolidated, and Europe is gradually losing its pharmaceutical productions, opening up areas of vulnerability which leads in severe cases to shortages. This cannot continue, and solutions must be found."

Christoph Stoller, President of Medicines for Europe, https://bit.ly/317V5U6

Virtual Support

EMA plans to help researchers and developers make better medicines

The EMA has launched an online scientific advice tool – IRIS – to give scientists easy access to guidelines on data integrity and regulatory procedures. Once registered on the platform, developers can access information related to orphan designations and parallel distribution, as well as search for Research Product Identifiers for new medicinal products. The EMA also encourages researchers to use the platform to apply for briefing meetings with its Innovation Task Force – a multidisciplinary group that offers scientific, regulatory, and legal advice.

The platform is a key part of the agency's "digital transformation process" and, though only launched in October 2020, plans for IRIS's expansion have already been made. The platform will be updated to cover a wider range of regulatory and scientific procedures. In the meantime, the regulatory body wants scientists to get to grips with the new tool and has published procedural guidelines to support its use.

GETTING A HANDLE ON HIGH POTENCY

Pharmaceutical products based on highly potent APIs (HPAPIs) are typically only needed in small doses, but their inherent potency presents pharma manufacturers with an important issue: safe manufacture. Here, four industry experts – John Fowler (Piramal Pharma Solutions), John Ross (Metrics Contract Services), Andrew Bulpin (Merck), and Maurits Janssen (Lonza) – explore the trends shaping the HPAPI market and discuss the challenges of working with these compounds.

WHAT TRENDS ARE EMERGING IN THE HPAPI MARKET?

Maurits Janssen: Pharma's quest for more effective drugs to improve patient outcomes has strongly boosted the number of HPAPIs in development pipelines. In general, when treating diseases, drug developers aim to influence the biological and biochemical pathways that cause them by blocking certain enzymes or cell receptors. As the market for oncology therapeutics grows – the sector accounted for 20 percent of global pharmaceutical sales for branded products in 2019 – it is increasingly important to develop potent molecules capable of killing cancer cells. But herein lies the challenge – small molecule drugs cannot discriminate between healthy and cancerous cells. By investing in targeted treatments, however, such as antibody-drug conjugates (ADCs), companies can avoid some of the conventional treatments' side effects and improve overall efficacy. This is because the API is carried directly to the treatment site. In some cases, these molecules are so potent that they can elicit therapeutic effects at lower doses.

John Fowler: As Maurits explains, HPAPIs are a rapidly growing segment in the pharmaceutical industry. The global market, which includes ADCs, is forecasted to reach nearly US$26 billion by 2022. Importantly, HPAPIs are very versatile. Post-formulation, they can be used as standalone therapies, as part of ADCs, or in combination therapies, such as immuno-oncology agents.

New molecular entities today are generally designed to be highly selective in their interactions with biological targets. And companies can manufacture HPAPIs with high levels of pharmacological activity using small amounts of active ingredients. These newer molecules remain active in vivo for longer, resulting in lower dosing frequency. The percentage of drugs classified as highly potent, with occupational exposure limits (OELs) of less than 1 mcg/m^3, has steadily increased.

Andrew Bulpin: Historically, HPAPIs were almost exclusively associated with oncology therapeutics. Today, there are a growing number of indications, classes of molecules, and new chemical entities that cover a much wider swath of the developmental pipeline, including programs being evaluated for inflammatory and antimicrobial/antibacterial indications. In tandem, the industry has continued to improve on its capacity to assemble, deliver, and harness the power of better medicines. In the past, many molecules were abandoned in preclinical or clinical trials because they were plagued with insurmountable safety and toxicity challenges. As an industry, we have increased molecular potency and specificity over time without impacting toxicity in patients.

John Ross: Another key trend involved in the HPAPI market is growth in outsourcing. A primary consideration for most companies in recent years is whether to outsource HPAPI manufacturing. There are myriad reasons companies choose to outsource including risk management, misalignment of production scale or facility utilization dynamics, and availability of contemporary approaches to HPAPI controls. A wide range of outsourcing providers have HPAPI capabilities, but this can make it challenging for companies to decide which partner is appropriate for their needs. Large CMOs may seem like an obvious choice because they offer the highest production volumes but, given the nature of HPAPIs – higher potencies often mean that smaller dosage-unit volumes are required – the growth trend has been toward smaller-scale specialist partners.

Meet the Experts

JOHN FOWLER, CHIEF OPERATING OFFICER AT PIRAMAL PHARMA SOLUTIONS

John has almost three decades of industry experience and is currently responsible for operations and R&D) across all Piramal Pharma Solution sites in North America, Europe and Asia. Prior to Piramal, he was the Divisional CEO of the Global Fine Chemicals business at Johnson Matthey with responsibility for the services (custom API development, manufacturing, catalyst and chiral technologies), and products (generics development and manufacturing) portfolio. He holds a Chemical Engineering degree from Bucknell University, US, and an MBA from St. Joseph University, US.

JOHN ROSS, PRESIDENT AT METRICS CONTRACT SERVICES

John received a Bachelor of Science and an MBA from the University of Western Ontario. He has been in the pharmaceutical sector since 1995 and currently oversees the day-to-day business of Metrics, a CDMO specializing in novel drug development and the commercial manufacture of oral solid dose products. He is also responsible for the Metrics operation in Greenville, North Carolina, and Mayne Pharma's US Supply Chain, which includes a network of CDMOs.

ANDREW BULPIN, HEAD OF PROCESS SOLUTIONS AT MERCK

Andrew joined MilliporeSigma in 2006 and has over 30 years of experience in the life sciences marketing industry. He received his PhD in organic chemistry from Caen-Normandy University and his MBA from the University of Strathclyde. In MilliporeSigma's Process Solutions department, he helps customers develop, make, purify, and formulate medicines.

MAURITS JANSSEN, SENIOR DIRECTOR, STRATEGIC BUSINESS DEVELOPMENT, API DEVELOPMENT & MANUFACTURING AT LONZA

Maurits earned his PhD in organic chemistry from Utrecht University, the Netherlands, and subsequently held positions in the consulting, marketing and sales, and research and development sectors. With over 20 years of experience, he has worked across a broad portfolio of technologies for cGMP chemical and biological custom manufacturing from early stage to late phase/commercial, and gained significant experience with HPAPIs.

WHAT ARE THE CHALLENGES IN MANAGING HPAPI MANUFACTURING?

Ross: The industry has access to a wide range of containment solutions at various cost points that accommodate many unit operations and scales (discovery, laboratory, and commercial manufacturing and packaging). More containment solutions are developed each year and the costs of the technology are coming down. In the long term, the CAPEX required to manufacture HPAPIs in-house may be reduced, lowering the barriers to market entry. But for now, investment strategies for equipment and infrastructure must be balanced against the potential business opportunities available to an organization contemplating handling or processing HPAPIs. For pharma companies to manufacture in-house, significant investment – to remediate or retrofit uncontained equipment and sites for legacy products – would be required to meet today's regulatory expectations for safely handling HPAPIs.

Bulpin: There are certainly some major challenges for the industry to iron out when it comes to safe handling practices and containment technology. Companies must maintain, continuously assess, and potentially upgrade infrastructure, technology, and the expertise of employees charged with HPAPI development and manufacture. The market landscape and technology are continuously evolving, and companies must ensure that they are responding to and deploying state-of-the-art measures for handling HPAPIs to ensure worker safety.

Janssen: As Andrew mentioned, there is a lot of global capacity the pharmaceutical industry can tap into. Though many pharmaceutical companies have in-house capacity, manufacturing lines often suffer from low utilization. This can result from strategic decisions regarding market supply, projected volumes not following expectations or other issues. It also explains the recent trend of larger pharma organizations divesting some of their assets into smaller CDMO partners – but we've all seen examples where these types of move have failed to become profitable.

Seasoned players amongst the CDMOs have been following trends more proactively and have ongoing capital investment programs that will lead to expansions in the near future. From a global perspective, there is likely sufficient capacity available for HPAPIs, but one has to take a more situational view to identify the bottlenecks and capacity shortages in specific unit operations.

Fowler: In my view, CDMOs are best suited to HPAPI manufacturing. But companies and sponsors must foster strong relationships with their outsourcing partners to maintain control over outsourced activities because they often involve stringent safety requirements. Though mature CDMOs typically provide all the services required to satisfy the Chemistry, Manufacturing, and Control (CMC) section of an IND or NDA, HPAPI development and manufacturing is intrinsically complex and often needs to be performed using accelerated timelines (many of these NMEs are fast-tracked or have breakthrough status) to quickly address unmet medical needs. The more deeply involved companies can be with these processes, the better!

"The market landscape and technology are continuously evolving, and companies must ensure that they are responding to and deploying state-of-the-art measures for handling HPAPIs."

WHAT DOES THE IDEAL CDMO PARTNER OFFER?

Fowler: Companies should ask themselves several questions when looking for a strategic partner. Does the R&D staff include scientists and engineers with knowledge in the HPAPI space? Are appropriate engineering controls and procedures in place to safely handle these highly potent compounds? What cleaning and verification procedures prevent cross-contamination with other drugs in the facility? What is the CDMO's track record in terms of quality from an FDA perspective? Has the CDMO worked with potent compounds in the past and, if they have, at what phases of development and commercialization?

If your chosen CDMO partner doesn't satisfy all these criteria, look elsewhere.

Ross: Outsourced production transfers much of the risk, resource investment, and material handling complexity onto the contract partner. Notably, smaller CMOs typically work at a kilo-scale; this is a key component of risk mitigation because HPAPIs can be incredibly costly.

When it comes to HPAPI development and manufacturing, the services on offer will vary greatly between CDMOs. Some will only be interested in larger-scale manufacturing work, whereas specialized partners can be more embedded in a product's success. Look for a partner that can offer support at all phases of a product's journey, from formulation development, and analytical services, right through to the clinical stages and commercial manufacturing. It's about thinking holistically about a drug's lifecycle and troubleshooting challenges during formulations to ensure manufacturability and downstream success.

The most important thing to look for in potential partners is whether they have the proper equipment, facilities, and infrastructure to handle HPAPIs based on their known potency, and potential health and safety hazards. The CDMO must also understand the various risks associated with different unit operations and scales, and be able to articulate a suitable plan to mitigate those risks. Before a project begins, important groundwork must be laid. Each HPAPI must be properly categorized and control-banded according to its hazards by a certified toxicologist or industrial hygienist before introducing a new product into a specific facility. This step assists with determining the optimal level of containment investment needed for the HPAPI and whether the partner has the capabilities to deliver the work. OEL and acceptable daily exposure values should also be obtained from a certified toxicologist at an early development stage to promote the selection of containment equipment, along with safe handling and processing of HPAPIs.

Importantly, contained equipment and facilities should always be considered upfront when discussing specific handling and processing steps needed to work with HPAPIs and meet best practices in handling such materials.

Janssen: The biggest challenge for producers, whether CDMOs or pharmaceutical companies, is ensuring all necessary safety precautions during the manufacturing process are carried out. They must employ special measures to protect their employees during the manufacture of these high-potency drugs. These measures are different for different parts of the manufacturing chain (e.g., drug substance, drug product), which may necessitate additional investment in primary and secondary containment measures, as well as additional training for employees. These efforts can, in turn, extend the duration of a clinical program or time to market approval. Working with a partner who has an integrated offering across the manufacturing chain can avoid these challenges and optimize supporting products that are awarded an accelerated approval option.

HOW DO CDMOs PREPARE THEIR EMPLOYEES FOR SAFE HPAPI HANDLING?

Ross: There is a wide variety of containment technologies and equipment available. From split butterfly valves to isolators to "bag-in, bag-out" filters, employers must ensure that their staff are confident in their use and fully understand the hazards. The training they provide shouldn't be limited to machinery. The workforce needs to have a rounded understanding of the best practices needed to handle HPAPIs safely.

I believe it is beneficial if these learning experiences are hands-on, with visual demonstrations of containment technologies and work practices. Discussion should always be encouraged as it helps staff get to grips with containment and work practice failure modes – critical in reinforcing learning outcomes and instilling the "why" of proper containment and handling practices.

Bulpin: Proper training and state-of-the-art equipment are integral parts of preparing employees for HPAPI handling – but safety procedures must also be designed into manufacturing processes with concerted efforts focused on eliminating or minimizing unit operations that can compromise safety, risk cross-contamination, and complicate cleaning procedures.

Janssen: Andrew is right – companies need to establish a strong safety culture throughout their organizations and operations, independent of the type of compounds handled. Making safety everybody's responsibility provides employees with the right mindset to handle pharmaceuticals with normal or high potency properties appropriately. Potency is not a binary property of compounds but represents a continuum that requires increasing levels of organization, technical tools, and measures to allow employees to work in a safe environment. To apply these measures correctly, employees should expect to receive – and employers should proactively offer – appropriate training on safety procedures, containment strategies, and operational handling of HPAPIs from their employers before being confronted with such a situation.

The whole effort should be supported by a company's health, safety, and environment (HSE) team. When a new asset or type of unit operation is introduced, verification tests with a surrogate compound of low toxicity that can easily be detected and analyzed – like lactose, mannitol, or naproxen sodium – should be conducted following appropriate ISPE/SMEPAC guidelines. During these tests, unexpected situations should also be simulated. Once evaluations prove that the asset or operation performs to the required specification, this occupational hygiene testing should be continued throughout the initial phase of operation with the specific highly potent compound. Such testing should be conducted especially for compounds with higher potency than previously handled. Results should be openly shared and discussed between employees, operational management, and HSE.

A good practice to ensure sustainable success from the start is the early involvement of experienced employees.

Their input and recommendations should be taken seriously and the necessary measures should be implemented. Finally, periodic verification testing and experience exchange between employees, operations, and HSE will ensure a sustainable and safe operation in the long run.

HOW IS THE REGULATORY ENVIRONMENT AROUND HPAPIS CHANGING?

Ross: Regulatory controls around HPAPI manufacturing have grown more robust over time. One key change has been that companies are now asked to rely on engineering controls rather than on standard work practices and personal protective equipment (PPE) to reduce exposure to HPAPIs. Regulators worldwide have also placed increased focus on cross-contamination and proper facility design for multi-product operations that process HPAPIs. These trends have created some additional requirements around cleaning and validation; most companies are responding by exploring single-use technologies and systems.

Environmental agencies are also heavily involved and require the reduction – or, in some cases, elimination – of HPAPIs in process wastewater systems. Some countries have established performance-based limits using ecotoxicology data for HPAPIs, whereas other agencies require risk assessments for HPAPIs released into the environment and reduction of unacceptable risks through various mitigation strategies. All of these aspects of development require significant investment. They also impact business terms for installing and providing services for HPAPI drug products.

Janssen: Regulatory requirements around containment, personnel safety, and responsible waste processing are not changing substantially. There may be differences from country to country, and as long as engineering controls go before policies and policies go before PPE when handling HPAPIs, there isn't a problem. When robust training is implemented, it should help companies deliver on adequate protection and sustainable operations.

However, the regulatory environment for active pharmaceuticals is changing with the increase in regulators' granting accelerated approval pathways – especially in oncology. In early development, there is often insufficient toxicology data to determine the OEL at which the compound should be contained, so companies should follow a more conservative approach to containment. HSE teams worldwide are defining OEL in development phases based on computer simulations, similarities to known compounds, or simply by defaulting to highly potent compounds in the first place and only relaxing constraints when more toxicology data is available.

WHAT ARE YOUR RECOMMENDED BEST PRACTICES FOR HPAPI CONTAINMENT AND HANDLING?

Fowler: Facility design and engineering controls are key. Robust heating, ventilation, and air conditioning systems (HVAC), state-of-the-art approaches to barrier isolation, incorporation of gowning areas, and significant personnel training are all essential. Continual education and training of chemists, engineers, and operators is crucial to ensure that they are aware of risks and are intimately familiar with the use of engineering controls, PPE, industrial hygiene protocols, and standard operating procedures (SOPs). Without highly skilled personnel, safe and effective HPAPI production will be a challenge, even in the most advanced facilities.

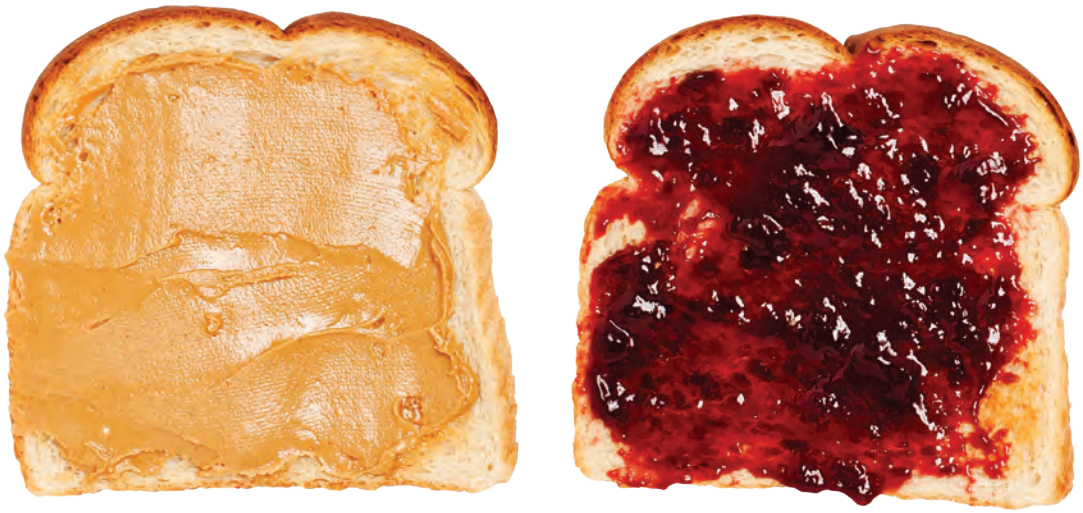
Ross: In my opinion, the best practices for HPAPI containment and handling are those that can be implemented during the concept and design phases for equipment and facilities to keep the costs of these systems in check. Retrofitting containment solutions and handling practices after a piece of equipment has been purchased or after a facility has been built is expensive and unsustainable.

Janssen: I agree with the previous responses, but would add that CDMOs need to integrate containment strategies into their risk analyses and technical transfer processes. We can achieve this by aligning unit operations with defined primary and secondary containment, and by conducting gap analyses on the design concepts. It's also essential to get cleaning and decontamination procedures right.

There truly is a great advantage in working with reputable players in the HPAPI area. There is also an increasing trend toward players that can support manufacture on both the drug substance side and the formulated finished product in an integrated manner. Such a partnership structure often aligns with the accelerated timelines expected for these specialty medicines.

> *"A good practice to ensure sustainable success from the start is the early involvement of experienced employees."*

Some things just go together.



LIKE OUR NP-RD10A TABLET PRESS & NATOLI AIM™*Pro* SOFTWARE

THE PERFECT MATCH, *NOW AT A PERFECT PRICE.*

Pair peanut butter with jelly and the result is amazing taste. Pair the Natoli **NP-RD10A** bench-top single station tablet press with our tried and proven **Natoli AIM™*Pro*** software and the result is amazing, **PLUS** you'll ***get $3,000 off!***

KEY BENEFITS OF THE PERFECT MATCH:

- Save time by getting projected tablet data results from even minor formulation changes
- Export compression force, ejection force, and other tablet data directly from the NP-RD10A tablet press
- Permits independent control of tablet hardness and weight
- Plot tableting and formulation characteristics in order to eliminate or mitigate potential tableting deficiencies
- Generate tabletability, compactability, and compressibility data from a single tablet, allowing use of a minimum amount product formulation
- 85 kN force capacity for easy tablet compression

Request a FREE live demo of our tried and proven Natoli AIM™ software today!

MANUFACTURED IN THE UNITED STATES OF AMERICA

YOU DEMAND. WE DELIVER.

NATOLI ENGINEERING COMPANY, INC.

natoli.com • info@natoli.com • +1 636.926.8900

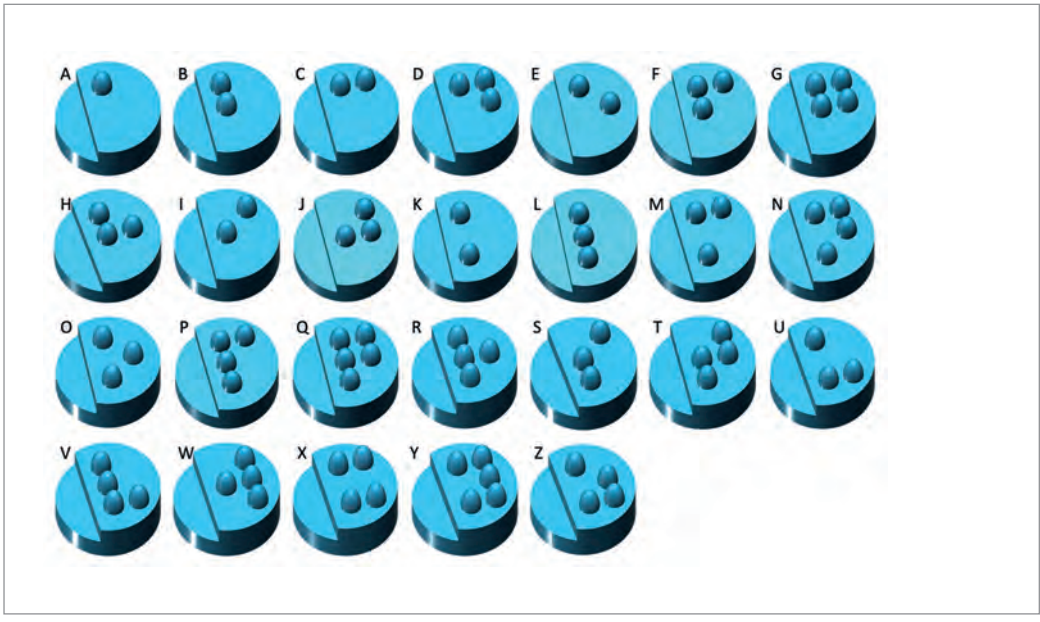
NATOLI

The Next Big Thing?

A Tactile Experience

How can we improve medication adherence among blind and partially sighted patients?

For Atheer Awad, 3D printing is at the heart of modernizing the pharmaceutical industry. The University College London researcher works alongside FabRx, a biotech focused on the development of pharmaceuticals and medical devices, on the manufacture of medicines that cater to specific patient needs. Now, Awad and her colleagues are using their platform to customize medicines for the visually impaired – a patient demographic that suffers more than its fair share of medical errors and poor adherence.



What challenges do visually impaired people face when taking medication?

More than 80 percent of blind patients are over 50 and many live with multiple chronic diseases. One of the main challenges for these patients is their inability to identify their medications when taken out of the original packaging. How are visually impaired people expected to distinguish between different types of medicines when they are all of similar shapes and sizes? These challenges pose a serious problem for patient compliance, potentially resulting in low medication adherence and increased medication errors, which could lead to poor treatment management, reduced therapeutic efficacy, and hospitalizations.

What did your research aim to achieve?

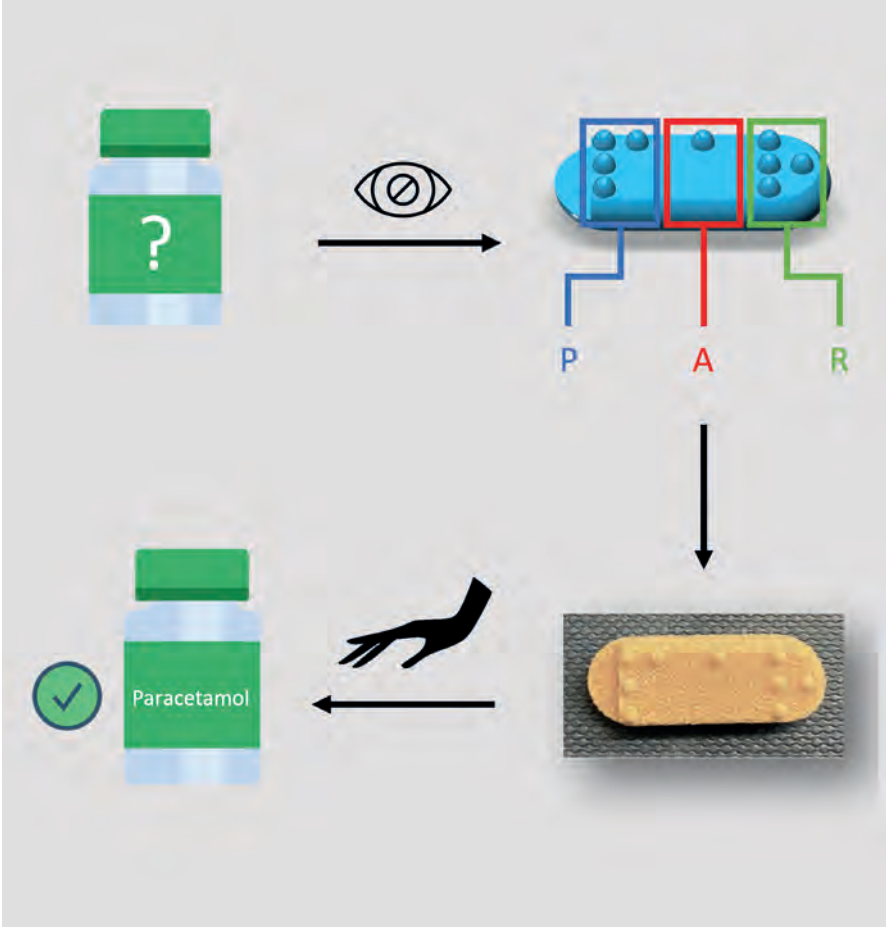
We wanted to create readable tablets for blind patients. Using selective laser sintering (SLS) – a 3D printing technology that uses a laser beam to superficially melt powder particles together using a layered approach – we developed orally disintegrating printlets with Braille and Moon alphabet patterns on their surfaces. We chose SLS because it is widely used to develop dosage forms with various release characteristics and intricate geometries. Despite the technology's advantages, we did have to optimize our printing parameters – including laser speed, and surface and chamber temperatures – to ensure that the mechanical properties of the printlets were not compromised. We managed to achieve excellent dissolution characteristics; all printed products disintegrated within five seconds, avoiding the need for water and facilitating their independent use. Most importantly, we verified the readability of the Braille and Moon patterns with a blind person – certainly a positive result for us!

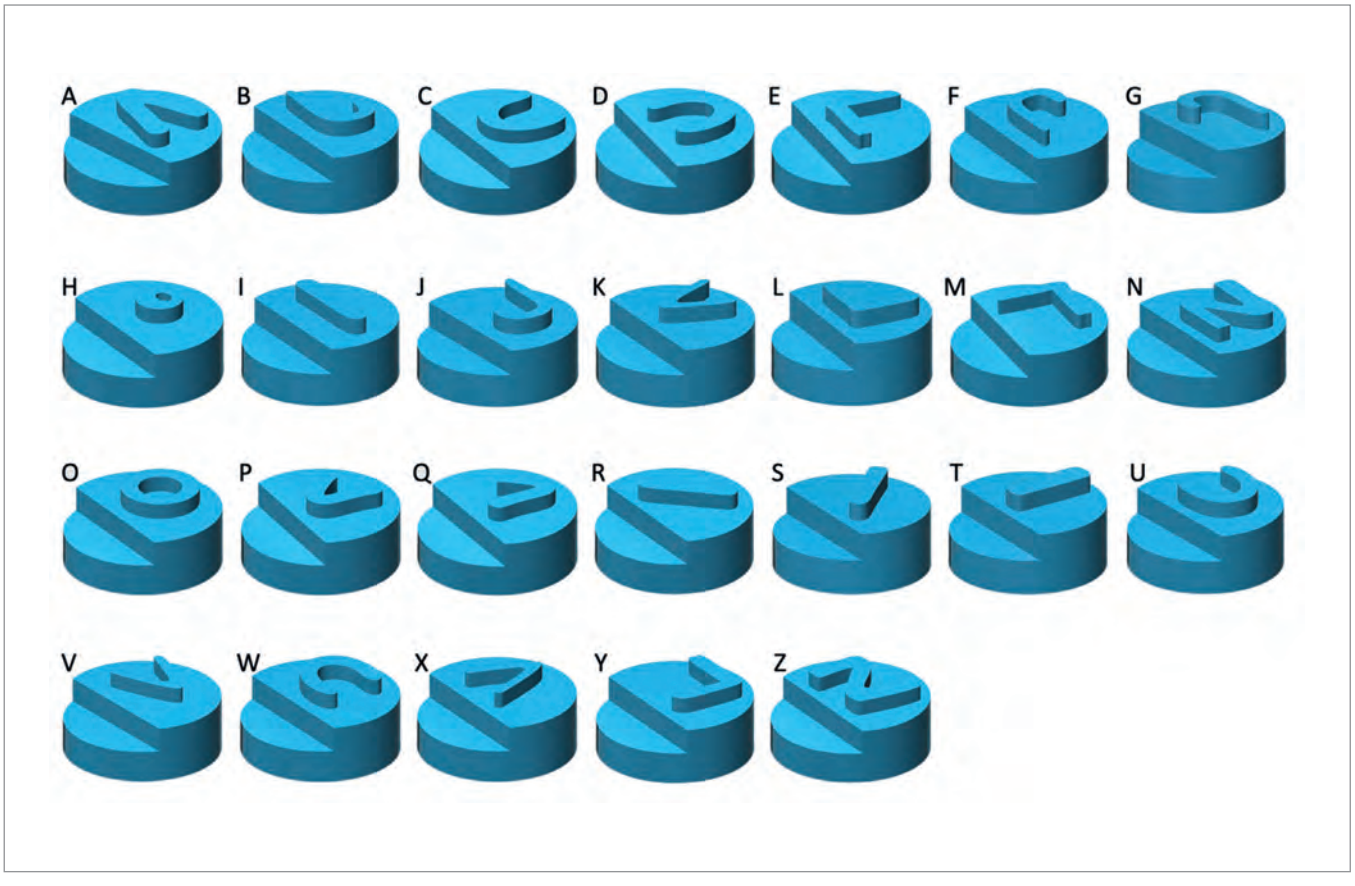
Put simply, our approach helps visually impaired patients distinguish between medications. Moreover, printlets with different shapes can be made to offer additional information, such as the disease indication or dosing regimen, ensuring that patients take their medications in accordance with their treatment schedules.

What's next?

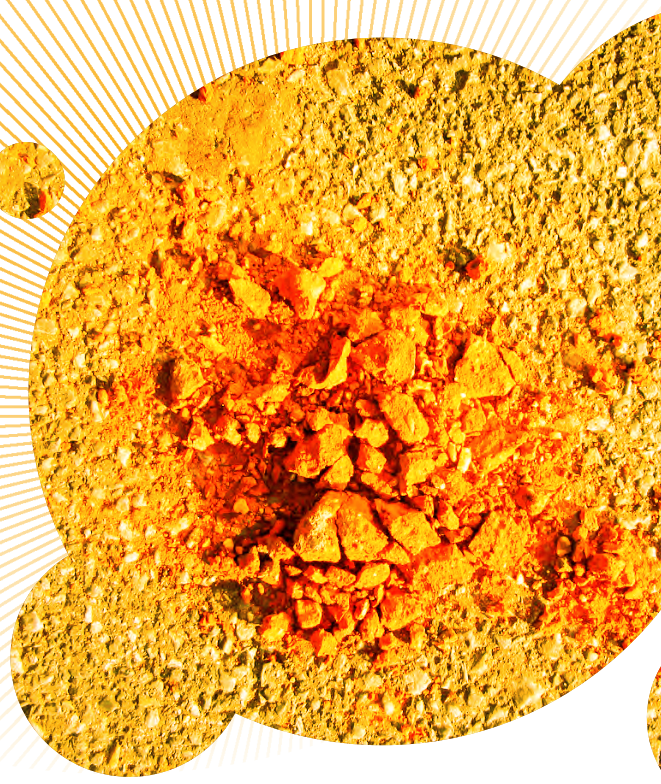
At the moment, we have only included three Braille letters on a printlet. Our design will have to be improved to enable the inclusion of more characters, which will ultimately help us provide patients with more detailed information. We also plan to print tactile patterns onto existing tablets, rather than 3D printing the whole formulation. That way, SLS 3D printing can complement existing pharmaceutical production techniques.

Although pharmaceutical 3D printing is still in its infancy compared with conventional production technologies, the results appear promising. We hope our research will help change the face of pharmaceutical manufacture by enabling enhanced transparency, medical efficacy, and safeguarding.





From Brick Dust to Blockbuster



How can we best deliver solubility-challenged small molecules to the clinic?

By David K. Lyon

The small molecule drug development landscape is changing. The number of complex, highly potent compounds taken to clinical trials and market is increasing, largely driven by biopharma oncology and immunology portfolios (1). Furthermore, smaller companies drive much of the innovation – not only in taking molecules to the clinic, but also to commercialization – although they usually lack the "bricks and mortar" necessary to bring a compound to market alone (2). Additionally because of the breakthrough designations, many molecules successful in the clinic follow accelerated timelines. This can put additional pressure on defining the supply chain to meet product timing. Finally, many new products, whether they are first-in-class or fast-followers, face uncertain market demand once approved, which leads to difficulties in forecasting market uptake and peak market demand.

A simultaneous trend in small molecule development is the continuing increase in low-solubility compounds (3). Low-solubility compounds cannot be orally absorbed and therefore cannot have a therapeutic effect. There are many technologies drug developers can use to address molecule complexity and bioavailability challenges, but taking a trial-and-error approach to technology selection can be time-consuming and costly. A better approach is to analyze the optimal technology based on a compound's physical, chemical, and biological properties. This method can help speed the delivery of more solutions to patients in need.

Working with the insoluble

Experts say as many as 70–90 percent of compounds in the pharmaceutical pipeline can be poorly water-soluble. The low solubility of these complex molecules can be driven by poor dissolution or can be truly solubility-limited due to either the lipophilicity of the molecule or high crystal forces that inhibit dissolution. These types of compounds are often

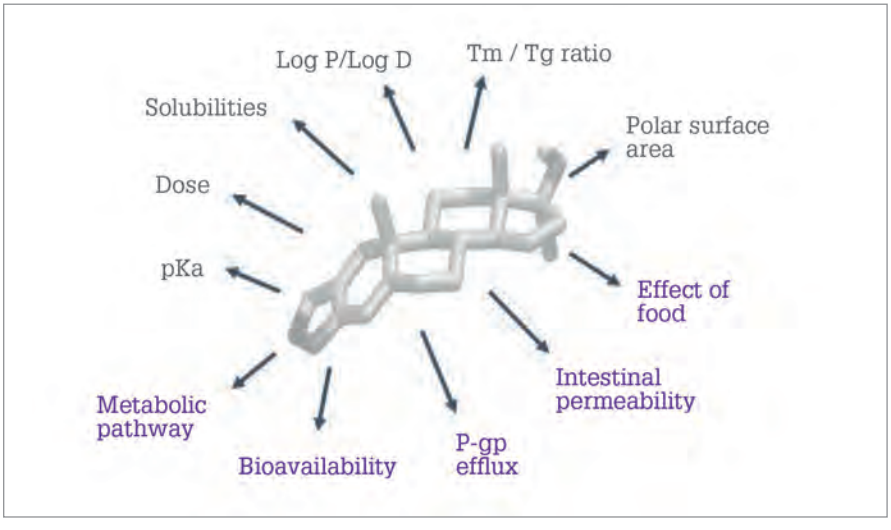
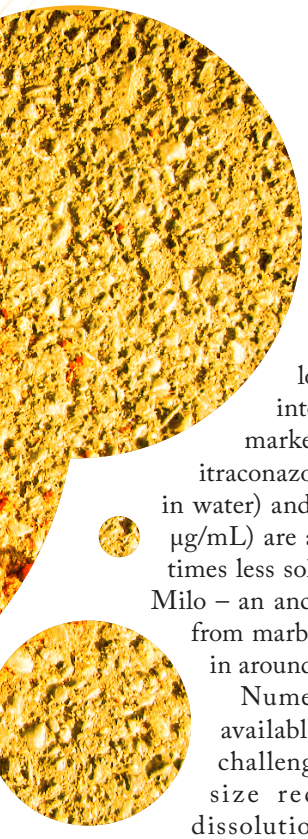


Figure 1. Physical-chemical-biological properties considered in a compound and property qualification scheme.



referred to as "grease ball" or "brick dust" compounds.

To put the concept of low-solubility compounds into context, commercially marketed compounds such as itraconazole (~1–4 ng/mL soluble in water) and abiraterone acetate (~1 µg/mL) are approximately 10–1,000 times less soluble than the Venus de Milo – an ancient Greek statue made from marble that has not dissolved in around 2,000 years.

Numerous technologies are available to address solubility challenges, including particle size reduction to increase dissolution rate; complexation using cyclodextrins to increase effective solubility; lipid-based formulation (LBF) delivery; or amorphous solid dispersions (ASD) to increase both dissolution rate and solubility (5). Of these technologies, the most common in commercial use in the past decade are LBFs and ASDs (6).

Due to the vast number of potential technologies used to advance a compound, the pathway from preclinical drug substance to clinical-ready dosage form is complex and costly. This is especially true if it follows a trial-and-error approach to formulation and technology evaluation. Avoiding trial-and-error requires formulators to address a multifaceted problem – but this can be done by considering the molecule's physical-chemical-biological properties (compound and property qualification), decision trees, high-throughput screening, in silico approaches, and the use of guidance maps (7, 8, 9, 10).

In principle, science-based methods can lead to rational formulation selection. However, methods based on

"Experts say as many as 70–90 percent of compounds in the pharmaceutical pipeline can be poorly water-soluble."

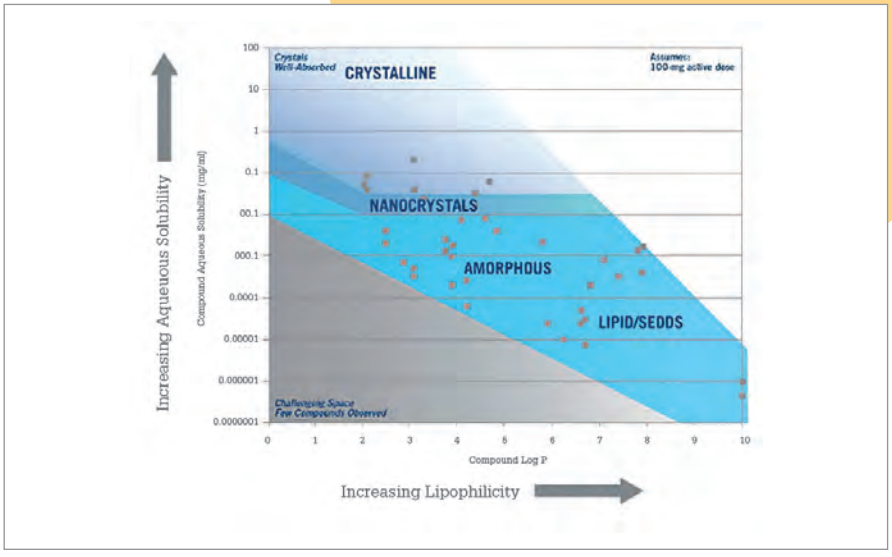


Figure 2. Guidance map showing technology applicability as a function of aqueous solubility and lipophilicity.

Compound property	*Value*
Log P	5.12
Aqueous solubility	1 µg/mL
T_m	147-148 °C
PK_a	5.2 (base)
Permeability	Low, non P-gp substrate
BCS class	Class IV at current dose

Product feature	*Zytiga (Janssen)*	*Yonsa (Churchill)*
Use	Metastatic castration-resistant prostrate cancer	
Dose	1000 mg (4 x 250 mg tablets)	500 mg (4 x 125 mg tablets)
Enabling technology	None	SoluMatrix
Bioavailability	<10%	<25%
Food-label	Yes	No
Effect of food on absorption	10-fold ↑ in AUC, 17-fold ↑ in Cmax	4.4-fold ↑ in AUC, 6.5-fold ↑ in Cmax

Table 1. Physical chemical and biological properties for abiraterone acetate (1).

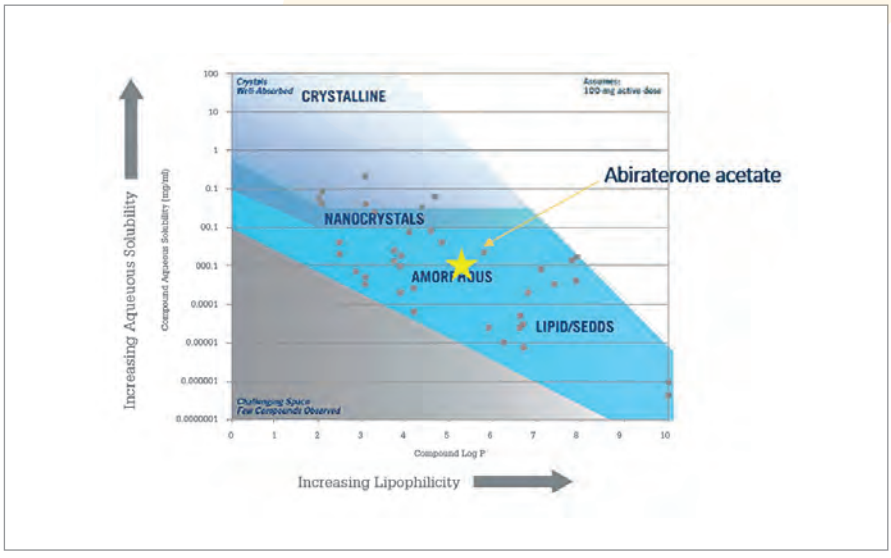


Figure 3. Abiraterone acetate plotted on a solubility-lipophilicity guidance map.

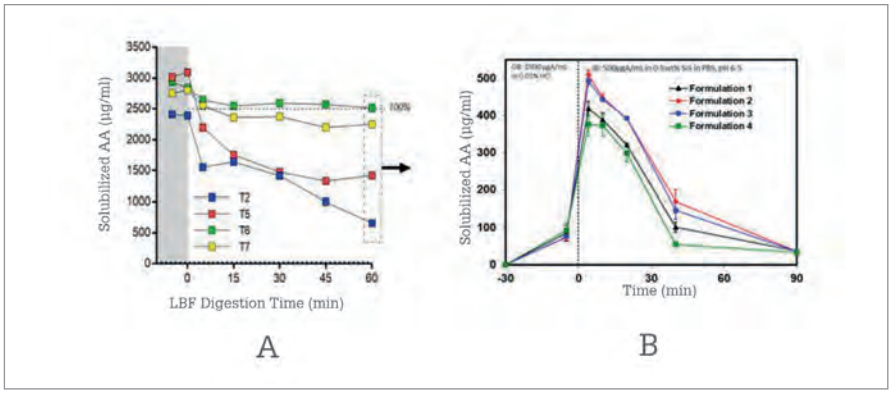


Figure 4. In vitro testing of abiraterone acetate LBP (A) and SDD (B) formulations.

fundamental knowledge of a compound's physical-chemical-biological properties (compound and property qualification) or on extensive experience with a broad range of compounds (guidance maps) can lead to an optimal formulation faster. When using compound and property qualification, we consider an aggregate of compound properties (see Figure 1) to determine the appropriate formulation to progress.

For example, if a compound has a high melting-point-to-glass-transition-temperature ratio, the compound is likely to crystallize rapidly. Therefore, an ASD is likely to be the technology of choice. However, if a compound is highly lipophilic or is transported via a P-glycoprotein efflux mechanism, then an LBF would be more appropriate.

The guidance map approach uses physical-chemical properties to map technologies onto a chemical space. The map in Figure 2 plots aqueous solubility as a function of lipophilicity and shows regions where specific technologies are expected to provide an optimal formulation. As noted above, highly lipophilic compounds, which often have high lipid solubility, tend to be more appropriate in an LBF formulation.

Two case studies illustrate the use of compound properties and guidance maps.

"The pathway from preclinical drug substance to clinical-ready dosage form is complex and costly."

Case 1: LBF vs. ASD for a "grease ball" compound

Abiraterone acetate is a prostate cancer treatment marketed by Janssen Pharmaceuticals as Zytiga. The physical-chemical properties are listed in Table 1 and its position on a representative guidance map is shown in Figure 3.

In Figure 3, it appears that abiraterone acetate would be preferentially formulated as an amorphous form. However, when the physical-chemical properties are examined, the compound's lipophilicity, moderate melting point, low permeability, and positive food effect suggest that it may be a suitable candidate for LBFs.

To validate the technology selection criteria, abiraterone acetate was formulated using best practices as both an LBF and an ASD. These formulations were then evaluated using in vitro methods (see Figure 4) – a lipid digestion test for the LBF and a non-sink dissolution test for the ASD (11, 12).

An LBF was successfully prepared to sustain a supersaturated drug concentration for more than 60 minutes, whereas the ASD formulations became supersaturated and precipitated after about 45 minutes.

Based on these in vitro data, the best formulations from each technology class were implemented into a fasted beagle

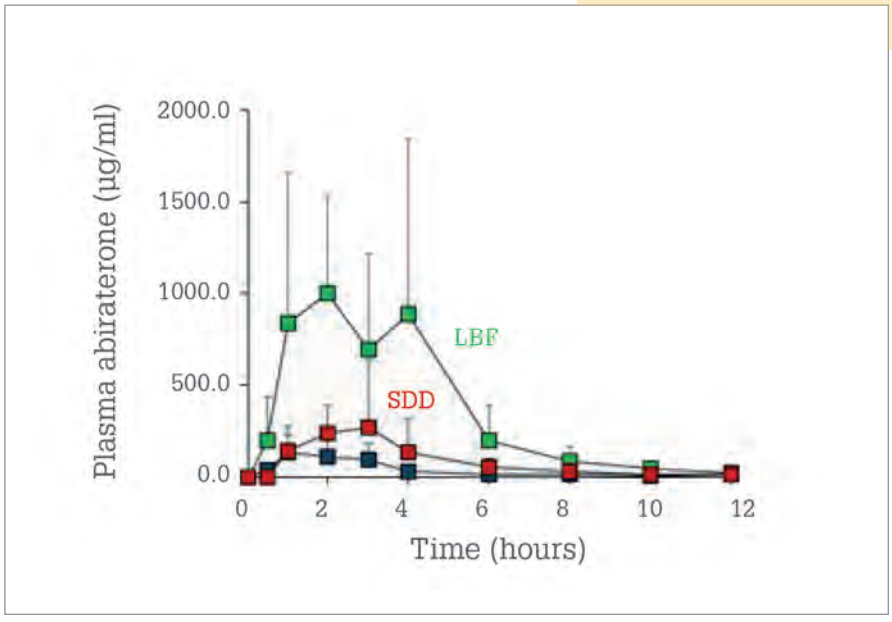


Figure 5. In vivo plasma concentrations for abiraterone acetate as a function of time in beagle dogs for LBF (green) and ASD (red) compared with the reference product (blue).

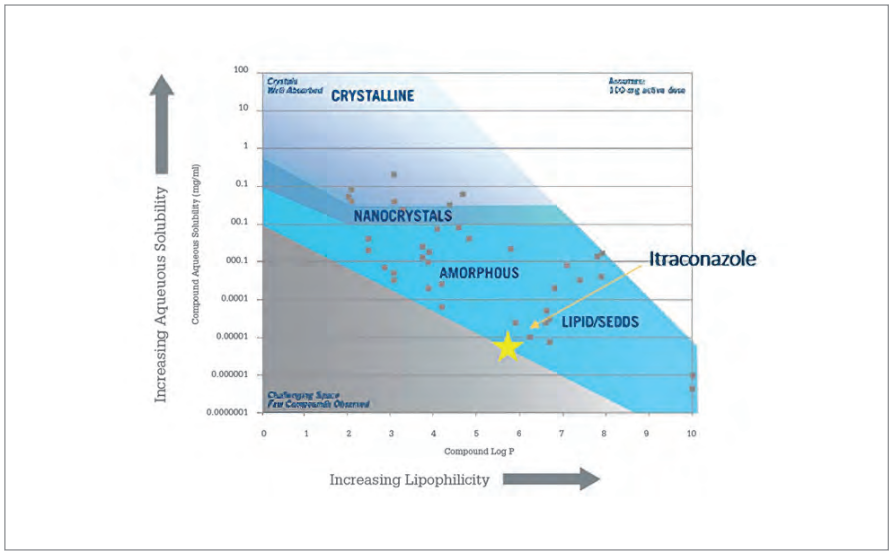


Figure 6. Guidance map of itraconazole as a function of solubility and lipophilicity.

dog study. The results from the dog study are shown in Figure 5.

The LBF formulation's performance was clearly superior to those of both the ASD and the reference product. The relative exposure increase was about 10-fold for the LBF and twofold for the ASD compared to the reference product. This emphasizes the need for careful evaluation of a compound's physical-chemical properties when choosing the proper bioavailability-enhancing technology.

Case 2: The optimal spray ASD for a "brick dust" compound

In this case, research sought to determine the optimal formulation technology for itraconazole, marketed by Janssen Pharmaceuticals as Sporanox. Itraconazole appears to fall into a region that would favor an LBF (see Figure 6). However, the molecule's low solubility in water, lipids, and solvents rules out a lipid solution and only allows for suspensions – which were significantly outperformed by the reference product in vivo in a rat study (13).

Because the reference product was already formulated as a hydroxypropyl methylcellulose (HPMC) dispersion, the question became, "Could an improved amorphous dispersion be designed?" ASD formulations were prepared and evaluated using a material-sparing membrane permeability in vitro test (14). The itraconazole concentrations in the receiver phase of the membrane permeation test are shown in Figure 7.

Based on these tests, a hydrophobic and a hydrophilic ASD were taken into an in vivo rat study (see Figure 8). The hydrophobic and hydrophilic SDDs outperform the reference product by approximately 50 and 125 percent, respectively (15).

These results also demonstrate that in vitro technology selection methodologies can predict superior-performing bioavailability enhancement technology based on a compound's properties and technology selection guidance maps.

Choosing your tech

Oral bioavailability-challenged molecules are still present in large numbers in pharma and biotech pipelines. Multiple technologies can improve compound oral bioavailability, with LBFs and ASDs often most appropriate for grease ball compounds (such as abiraterone acetate) and ASDs for brick dust compounds (such as itraconazole). But, for each compound, we need rational technology selection to optimize performance, smooth development, and

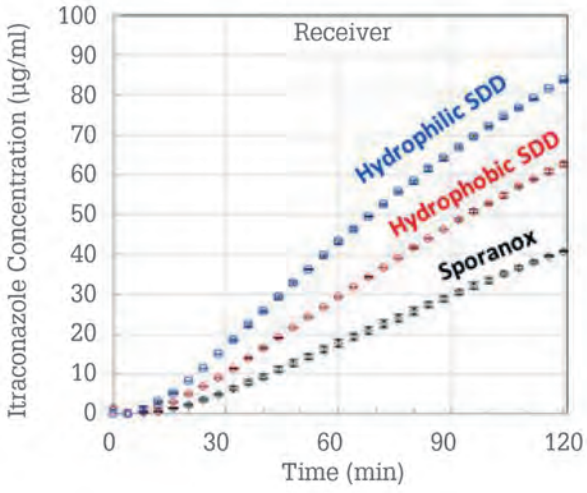


Figure 7. Membrane permeation results for three itraconazole ASDs.

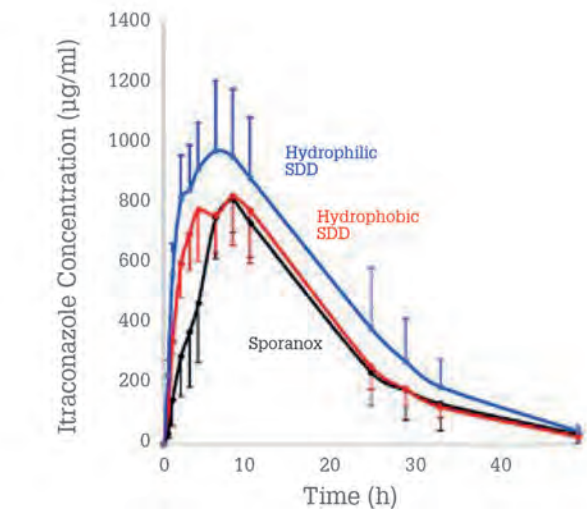


Figure 8. Plasma concentrations of itraconazole as a function of time and ASD formulation.

avoid overuse of precious resources. Validating a technology selection process also requires in vivo data – and there is currently no single in vitro method that can adequately compare all the different technologies.

David K. Lyon is a Senior Research Fellow at Lonza, Bend, Oregon, USA

References

1. *G Miglierini, "Emerging trends for the pharmaceutical market", (2019). Available at: https://bit.ly/2Thp8EL*
2. *Lonza Internal Market Analysis*
3. *BJ Boyd, "Successful oral delivery of poorly water-soluble drugs both depends on the intraluminal behavior of drugs and of appropriate advanced drug delivery systems," Eur J Pharm Sci., 137 (2019).*
4. *S Kalepu and V Nekkanti, "Insoluble drug delivery strategies: review of recent advances and business prospects", Acta Pharma Sin B,5, 442, (2015).*
5. *HD Williams et al., "Strategies to Address Low Drug Solubility in Discovery and Development", Pharmacol Rev, 65, 315, (2013).*
6. *S Ali and K Kolter, "Challenges and Opportunities in Oral Formulation Development", Pharm Rev, 15, 1, (2012)*
7. *GA Fridgeirsdottir et al., "Support Tools in Formulation Development for Poorly Soluble Drugs", J. Pharm Sci, 105, 2260, (2016).*
8. *W-G Dai et. al., "Advanced screening assays to rapidly identify solubility-enhancing formulations: high-throughput, miniaturization and automation," Adv. Drug Delivery Rev. 2008, 60 (6) 657-672 (2008).*
9. *CA Bertrom et al., "Early pharmaceutical profiling to predict oral drug absorption: current status and unmet needs", Eur J Pharm Sci, 57, 173, (2014).*
10. *DT Friesen et al., "Hydroxypropyl Methylcellulose Acetate Succinate-Based Spray-Dried Dispersions: An Overview", Mol Pharm, 5, 1003, (2008).*
11. *B Wu, J Li, Y Wang, "Evaluation of the Microcentrifuge Dissolution Method as a Tool for Spray-Dried Dispersion," The AAPS Journal, 18 (346-353 (2016).*
12. *HD Williams et al., "Toward the establishment of standardized in vitro tests for lipid-based formulations, part 1: method parameterization and comparison of in vitro digestion profiles across a range of representative formulations", J Pharm Sci, 101,3360, (2012).*
13. *Y Sahbaz et al., "Transformation of poorly water-soluble drugs into lipophilic ionic liquids enhances oral drug exposure from lipid based formulations", Molecular Pharmaceutics, 12, 1980, (2015).*
14. *AM Stewart et al., "Development of a Biorelevant, Material-Sparing Membrane Flux Test for Rapid Screening of Bioavailability-Enhancing Drug Product Formulations", Mol Pharm, 14, 2032, (2017).*
15. *AM Stewart et al., "Impact of Drug-Rich Colloids of Itraconazole and HPMCAS on Membrane Flux in Vitro and Oral Bioavailability in Rats, Mol Pharm, 14, 2437, (2017).*

GEA Group

ConsiGma 4.0: Next-generation continuous manufacturing

Committed to "engineering for a better world," GEA has expanded, integrated and consolidated its ConsiGma® portfolio of continuous oral solid dosage granulation, drying and tablet compression equipment.

Based on three key pillars, the multipurpose ConsiGma® 4.0 platform — designed to transfer powder into coated tablets in development, pilot, clinical and production volumes — can now be supplied as

- a fully integrated line
- standalone plant for dedicated "bin-to-bin" unit operations
- a combination of modules that can be installed in both new and existing facilities with selected and qualified third-party machinery.

GEA can provide top-of-the-range, fully configurable manufacturing systems that convert powder into coated tablets in a single line, as well as customer-specific equipment that can be integrated with existing plant. Irrespective of the size or scale of your CM implementation strategy, GEA's SCADA-compliant ConsiGma® "Conductor 4.0" control software facilitates the integration and consolidation of independent unit operations.

CONTACT: *GEA Process Engineering nv, Keerbaan 70, 2160 Wommelgem, Belgium*

WEB: *www.gea.com*

Adapting to Change

Sitting Down With… Kimberly Eggers, Vice-president of Medical and Clinical Affairs, Aprecia, Blue Ash, Ohio, USA

Why did you choose a career in pharmacy?

I've always believed that a career in healthcare was right for me. I have a love of math and science and, from an early age, I wanted to help care for people. But before I started college, I never truly considered a career in pharmacy – it was only during my freshman year that my eyes opened to the profession. I had the opportunity to shadow a pharmacist for a day and the experience helped me realize how well pharmacy aligned with my interests. This idea was reinforced during the time I spent working while at school. My first boss, Delane Long, was very invested in training students in his team. He showed us all what it meant to be a great pharmacist and care for patients well, and how to run successful businesses – the academic environment couldn't have provided such insight.

How did you come to join Aprecia?

Once my studies were complete, I took the tools I had developed and applied them to my role in retail pharmacy. It was a real privilege to be on the front lines of patient care and, despite transitioning into other areas of the industry as my career progressed, I still sought out ways of improving patient care. One way I pursued this passion was through the exploration of innovative clinical programs. I partnered with companies that were using technologies in unique ways and, in 2019, I was introduced to Aprecia. The company was founded in 2003 and was built on a 3D printing technology platform called ZipDose, which had been developed by Aprecia based on work that originated at MIT. Using binder jet printing, they manufactured flexible and porous dosage forms that rapidly disintegrated in the mouth – helping to tackle the real-life problems people experienced on a daily basis, such as swallowing difficulties and administering medicines to children. I had seen these challenges first hand in my previous role as a pharmacist! To-date, Aprecia remains the only company to have produced an FDA-approved 3D printed drug product. The drug, SPRITAM, is used in children and adults with certain types of epilepsy. The company's approach to manufacturing and patient care resonated with me and I joined their team later that year.

What most excites you about 3D printing?

The really exciting aspect is that there is no limit to what we can achieve using 3D printing technologies. And, as problems arise, they can be adapted to provide solutions. The pandemic has really helped prove this as companies have shifted their business models to print PPE and other essential items for healthcare workers and patients alike! Their timely response to the crisis would not have been possible using more conventional manufacturing practices.

But, beyond the challenges posed by the current pandemic, the promise of 3D printing technologies for pharma has yet to be fully explored. From personalized medicine to improved supply chains to designing dosage forms that enable improved outcomes and adherence, there's so much good that can come from 3D printing. We have a lot to look forward to in the years to come.

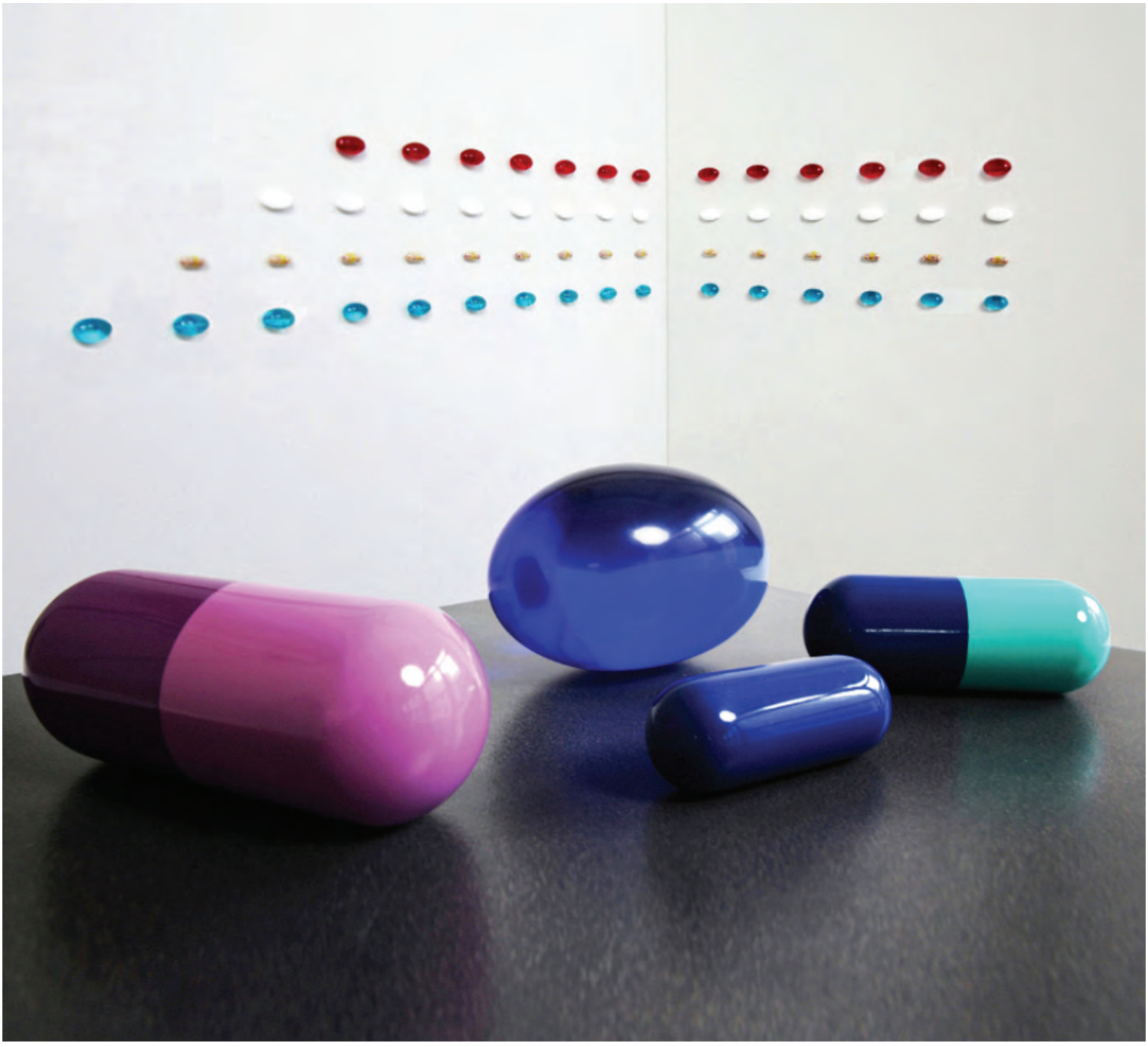
How has the pandemic affected your role?

I joined Aprecia in the summer of 2019 and so the latter half of my time at Aprecia has been unusual to say the least. Aprecia has certainly adapted to the challenges of COVID-19 and been a wonderful organization to work for. The pandemic has affected all our lives in different ways but, in my opinion, it has reinforced that good leadership is critical to the success of any organization. As a leader, when you invest in the right people and foster a positive work culture, it doesn't matter what you're faced with because you have a strong group of people around you to weather the storm. I also think it's important to focus on the good that has come out of this situation. The outbreak has forced us all to have new conversations and inspired us to think creatively about solutions to current and future problems.

"The outbreak has forced all of us to have new conversations and inspired us to think creatively."

What are your predictions for 2021?

That's a tricky question to answer! In general, predictions have gone out of the window, so we all have to expect the unexpected. But I hope that, as an industry, we don't lose sight of the core issues we've identified during the pandemic. I think it sometimes takes a crisis for people to sit down and assess what aspects of the healthcare industry need to be fixed. I also think there's a risk that, once we get out of this situation, we won't want to remember the stress and the trauma we've all experienced. I'm hopeful that we can stay focused on addressing the deficiencies in preparedness and patient care we're now picking up on so that we can face any future crises with robust plans in place.



PHARMACEUTICAL MANUFACTURING TECHNOLOGY IS SCIENCE. CUSTOMIZED SOLUTIONS AT THE RIGHT SCALE IS ART.

Successful product launches and reliable commercial supply are built on cutting-edge manufacturing science, seamless tech transfers, and the art of customized solutions at the right scale.

Catalent's track record in supporting hundreds of tech transfers and product launches every year, coupled with industry leading manufacturing technologies, customizable suites and flexible end-to-end solutions at the right scale, will help get your products, orphan or blockbuster, to market faster, turning your science into commercial success. **Catalent, where science meets art.**

Catalent®

US + 1 888 SOLUTION (765-8846) **EUR** 00800 8855 6178 catalent.com/manufacturing