Welcome .............................................................................................................................................................................. 3
Events Calendar 2020 .............................................................................................................................................................. 4-5
Industry News ........................................................................................................................................................................... 6-11
Pharma Enhancing drug efficacy using sustained-release coatings .................................................................................. 13-14
Pharmaceutical quality: concepts, misconceptions, realities and remedies .............................................................. 16-17
APs Overcoming the challenges of phyto-API supply .............................................................................................................. 18
Drug Development Grand Challenge 1: opportunities for partnership and investment ...................................................... 20-21
Drug Delivery Nanoforming: the new revolution ................................................................................................................... 22-23
Biologics The NevoLine platform: Enabling availability and affordability of biologics .................................................... 24-26
Natural Ingredients Tackling the diabetes pandemic ............................................................................................................... 29
Flow Chemistry Creating the ‘best fit for purpose flow reactor’ by 3D metal printing ............................................................. 30-32
Advantages of continuous flow synthesis ........................................................................................................................... 34-35
In full flow – continuously battling bacteria with boron .................................................................................................. 36-37
Cosmetics All-natural calcium carbonate particles for formulating personal care products .............................................. 38-39
An effective phytocannabinoid alternative to CBD ........................................................................................................... 41-43
Cosmetics sector experiencing higher demand for ‘clean beauty’ products ................................................................. 44-45
Coatings An introduction to the world of nanocoatings ........................................................................................................ 46-47
Contract Services Quality system management for CDMOs ................................................................................................. 48-50
Rethinking pharma packaging to better model shelf life ................................................................................................. 52-53
Catalysis Effectively crafting your process development .................................................................................................. 54

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At JM, we work globally with pharmaceutical innovators to deliver complex chemistry solutions for a healthier world. Our world-class knowhow, together with our portfolio of catalyst technologies, enables faster, cleaner and more efficient reactions. We leverage our leading capabilities in solid state sciences and particle engineering to produce sophisticated APIs and controlled substances and deliver novel treatments and medicines. Combined with our proven chemical and analytical development for scale up and production, we make a real difference to the quality of life for millions of people.

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Welcome

Events

Events Calendar 2020

Industry News

Pharma

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In full flow – continuously battling bacteria with boron

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Cosmetics sector experiencing higher demand for ‘clean beauty’ products

Coatings

An introduction to the world of nanocoatings

Contract Services

Quality system management for CDMOs
Rethinking pharma packaging to better model shelf life

Catalysis

Effectively crafting your process development
Azelis expands its global presence into Latin America

Azelis is thrilled to announce the acquisition of Megafarma, Mexico’s premier specialty distributor for the pharma, food and veterinary industries.

The addition of Megafarma into the Azelis global network strengthens our commitment to our valued principals and customers across Latin America, and is complementary to our strategy of sustainable organic growth. The transaction also creates a platform to build other market segments in Mexico, such as plastics, foam, CASE, personal care, and household & industrial cleaning.

Megafarma, headquartered in Mexico City, with offices in Guadalajara and Monterrey, represents some of the world’s most renowned raw material producers and serves a large number of customers throughout all regions of Mexico.

Innovation will help our industry lead the fight against COVID-19

Since our last editorial, the world has been hit by its greatest crisis since the onset of World War Two. The Coronavirus outbreak has already touched every corner of the planet and threatens to cause seismic disruption for months to come.

On one hand, the chemicals industry will play a key role in the fight against this menace. Pharmaceuticals firms are racing to find a viable antidote to COVID-19; sanitary products are now a must-have in every single home. However, we’re also facing huge challenges, as supply chains are severed and potential customers retreat into self-isolation.

In such a volatile climate, I can only praise the work of our staff, contributors and advertisers in delivering this latest edition. It is testament to the resilience of our team, and our industry, that we’ve been able to publish against such a challenging backdrop. We hope the latest content helps our readers make sense of the madness we’ve seen over the past few days.

Long-term, it’s impossible to predict how Coronavirus will change our industry. The pharmaceuticals sector will receive investment, for sure, and the shift towards better home hygiene will hopefully bring opportunities in personal care. But how will the agrochemicals sector react if, as expected, COVID-19 eats into global farming output? How will oil and energy companies bounce back from their recent market slumps?

The answer, inevitably, will lie in innovation.

The chemicals industry has always been a hotbed of ideas, and crisis has invariably roused its creativity. We saw that 100 years ago, when a huge influenza pandemic blitzed the world. The fledgling pharmaceuticals sector reacted with a relentless 25-year campaign of research and investigation, which ultimately delivered a successful flu vaccine.

The next few months, and years, will be an equally fertile period. We won’t just roll out new products; we’ll fundamentally change the way we work. Technologies like AI, big data and machine learning will be crucial, enabling chemicals companies to become leaner and stronger, empowering them to take the fight to Coronavirus.

These technologies will be crucial to the Chemicals Knowledge Hub, too. We’re launching an exciting new website next month, and our digital-first platform will help us react to the changing world in real time, giving our readers the jump on emerging trends. We’ll also remodel our events arm, to provide an even better service to our clients. The hub exists to connect our industry, and the current crisis has shown just how important this connection is.

The future certainly isn’t clear, but one thing seems certain: our industry is going to go through a period of evolution which will bring opportunities as well as risks. Yes, we are going to face huge challenges and frustrations, but we will also push towards a series of decisive breakthroughs.

There’s really no option but to press on. We may not be able to meet face to face, but the power of digital innovation will enable us to keep pushing forward.

Ellie Bruni
Publishing Director
Chemicals Knowledge Hub (Global)
<table>
<thead>
<tr>
<th>Event Name</th>
<th>Dates</th>
<th>Location</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIO International Convention</td>
<td>8-11 June 2020</td>
<td>San Diego, USA</td>
<td><a href="https://www.bio.org">Event Website</a></td>
</tr>
<tr>
<td>in-cosmetics korea</td>
<td>17-19 June 2020</td>
<td>Coex, Seoul, South Korea</td>
<td><a href="https://korea.in-cosmetics.com">Event Website</a></td>
</tr>
<tr>
<td>in-cosmetics global</td>
<td>30 June - 2 July 2020</td>
<td>Barcelona, Spain</td>
<td><a href="https://in-cosmetics.com/global/">Event Website</a></td>
</tr>
<tr>
<td>CPhI China</td>
<td>22-24 June 2020</td>
<td>Shanghai, China</td>
<td><a href="https://cphi.com/china">Event Website</a></td>
</tr>
<tr>
<td>in-cosmetics south east asia</td>
<td>1-3 July 2020</td>
<td>Muang Thong Thani, Thailand</td>
<td><a href="https://cphi.com/sea">Event Website</a></td>
</tr>
<tr>
<td>Interphex</td>
<td>15-17 July 2020</td>
<td>New York City, USA</td>
<td><a href="https://www.interphex.com">Event Website</a></td>
</tr>
<tr>
<td>Speciality &amp; Agro Chemicals America</td>
<td>28-30 July 2020</td>
<td>Charleston, USA</td>
<td><a href="https://charleston.chemicalsamerica.com">Event Website</a></td>
</tr>
<tr>
<td>Adhesive and Bonding Expo</td>
<td>25-27 August 2020</td>
<td>Seoul, Korea</td>
<td><a href="http://www.adhesivesandbondingexpo.com">Event Website</a></td>
</tr>
<tr>
<td>CPhI Japan</td>
<td>30 September – 2 October 2020</td>
<td>Osaka, Japan</td>
<td><a href="https://cphi.com/japan">Event Website</a></td>
</tr>
<tr>
<td>CPhI Middle East</td>
<td>14-15 September 2020</td>
<td>Abu Dhabi, UAE</td>
<td><a href="https://cphi.com/mea">Event Website</a></td>
</tr>
<tr>
<td>in-cosmetics Latin America</td>
<td>16-17 September 2020</td>
<td>Sao Paulo, Brasil</td>
<td><a href="https://latam.in-cosmetics.com">Event Website</a></td>
</tr>
<tr>
<td>APAC Biopolymer Summit 2020</td>
<td>16 – 17 September 2020</td>
<td>Kuala Lumpur, Malaysia</td>
<td></td>
</tr>
<tr>
<td>CPhI Worldwide</td>
<td>13 – 15 October 2020</td>
<td>Milan, Italy</td>
<td><a href="https://cphi.com/europe">Event Website</a></td>
</tr>
<tr>
<td>in-cosmetics North America</td>
<td>21-22 October 2020</td>
<td>New Jersey, USA</td>
<td><a href="https://cwhome.in-cosmetics.com">Event Website</a></td>
</tr>
<tr>
<td>in-cosmetics Asia</td>
<td>3-5 November 2020</td>
<td>Bangkok, Thailand</td>
<td><a href="https://asia.in-cosmetics.com">Event Website</a></td>
</tr>
<tr>
<td>TIDES EUROPE: Oligonucleotide &amp; Peptide</td>
<td>10-13 November 2020</td>
<td>Vienna, Austria</td>
<td><a href="https://www.informacqu.com/tides-europe/">Event Website</a></td>
</tr>
<tr>
<td>Chemspec Europe</td>
<td>11-12 November 2020</td>
<td>Cologne, Germany</td>
<td><a href="https://www.chemspeceurope.com">Event Website</a></td>
</tr>
<tr>
<td>In cosmetics formulation summit</td>
<td>11-12 November</td>
<td>London</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Bio Integrates</td>
<td>16 November 2020</td>
<td>London</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Pharma Integrates</td>
<td>17 November 2020</td>
<td>London</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>CPhI India</td>
<td>25-27 November 2020</td>
<td>Delhi, India</td>
<td><a href="https://www.cphi.com/india/">Event Website</a></td>
</tr>
</tbody>
</table>

For more information about these and other events in the speciality chemicals industry, visit [www.chemicalsknowledgehub.com/events](http://www.chemicalsknowledgehub.com/events)
New Class 6 manufacturing suite at BioSpectra

BioSpectra, Inc., a U.S manufacturer of premium pharmaceutical ingredients, has opened a new ISO Class 6 manufacturing suite for the production of sodium chloride solutions. The first product manufactured and shipped was a 5M NaCl solution made with multi-compartmented salting and injection, sterile filtered and filled into a sterile, custom bio-processing compatible, 1,000-litre container with satellite samples. The sodium chloride production suite is capable of manufacturing various molarities of NaCl and custom NaCl solutions and is the first of four, new ISO Class 6 manufacturing suites being built at the company’s 150,000 square foot, GMP facility in Bangor, Pennsylvania. The company has also begun its next major building expansion with plans to build a 40,000 square foot GMP warehouse for raw material and finished good storage in Wind Gap, Pennsylvania. Strategically located less than 20 minutes from the company’s two manufacturing plants in Stroudsburg and Bangor PA, this new facility will allow for further expansion of BioSpectra’s manufacturing footprint. Land has been purchased, and the past structure has already been demolished. BioSpectra will begin building the new warehouse with final approval from the local planning and zoning boards.

New strategy to combat SARS-CoV-2

The continuously increasing numbers of coronavirus infected patients and the death cases clearly show that there is no therapy against coronaviruses yet. Considering all available data on the effect of deuterium depletion on cell function and metabolism, and with more than 20 years’ experience with its Vetars-DDW 25 deuterium-depleted veterinary medicinal anti-cancer product, and with more than 20 years’ experience with its Vetars-DDW 25 deuterium-depleted veterinary medicinal anti-cancer product, and now deuterium depletion in pets.HYD LLC for Cancer Research and Drug Development plans to start preclinical and clinical studies to study the potential of deuterium depletion in viral infections. HYD LLC for Cancer Research and Drug Development has already conducted two prospective clinical trials on prostate cancer and metastatic diseases and possesses the necessary documentation to apply for ethical approval. Its parent company, HYD Pharma Inc, completed the first facility in the world to produce deuterium-depleted water (DDW) according to GMP rules for clinical trials. HYD LLC is looking for partners, sharing its IP for the development and common registration of drugs to treat the disease caused by the coronavirus. There is no warrant for the efficacy of deuterium depletion against the coronavirus, but the available research data and veterinary experience with DDW to create the firm basis for further investigations into the most promising therapeutical solution for the coronavirus pandemic within a reasonable time, the company said.

Univercells secures up to €50 million funding

Bioprocessing specialist Univercells has received up to €50 million in financing from Gaia Capital Partners (GCP), a new investment platform supported by leading global investment firm KKR, to develop next-generation bioprocessing technologies for the production of advanced biologic therapies including gene- and cell-based therapies. The investment will be deployed in a newly created subsidiary of Univercells focused on accelerating the industrialization and commercialization of the company’s manufacturing technologies, including the NevioLine biomanufacturing platform and the scale-X bioreactor portfolio. Specifically, the investment is intended to support continued expansion into the fast-growing gene therapy segment, including new developments that will enable a range of best-in-class solutions for viral manufacturing.

The transaction is expected to close in the first half of 2020. Once the transaction is complete, Univercells’ remaining businesses will concentrate on developing a portfolio of vaccines and biosimilars to be delivered at an affordable price and on establishing its services offering, and allowing easy absorption or remodelling by the human body. Univercells will use its established fermentation process technologies and global manufacturing network to commercialize the collagen platform for worldwide use. The platform will also support the company’s Tissue Engineering Project House launched in Singapore in 2018 by Evonik’s strategic innovation unit Creavis to develop advanced biomaterials solutions in regenerative medicine.

CatSci appoints industry-renowned leadership team

Award-winning process research and development firm CatSci, which has appointed a new senior leadership team as part of its strategic expansion in supporting global innovator Pharma to meet growing clinical manufacturing and contract (CQS) needs. The company says that these key members of staff will enable the captivating designers to focus on ancillary strategy, building upon CatSci’s continued growth, which will help to balance the company’s mission of delivering affordable, best-in-class small molecule therapeutics with the vision of striving to create 500 high-value jobs by 2030. The new CatSci leadership team is as follows: Dr Alan Steven, Senior Principal Scientist, who has more than 30 years of experience with AstaZineca in designing manufacturing processes and control strategies for small-molecule APIs; Dr Mark Waring, General Manager, who joined CatSci with more than 20 years of experience in manufacturing and the CRO environment. After a period of integration, Dr Waring will assume full responsibility for the business unit, including PUL, and Dr Sam Whitman, Head of Process Research and Development, who brings 15 years of analytical and leadership experience from past roles at BP and AstraZeneca. In his new position, he will lead the technical function with accountability for delivering greener, safer and more cost-effective process research and development services.

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Evonik biotech breakthrough: new animal-free fermentation-based collagen platform

Evonik has developed an advanced collagen platform made using fermentation-based processes devoid of animal or human-derived materials using recombinant technology to produce a highly soluble, ultra-pure product that is safe, sustainable and commercially scalable. The proprietary platform features a triple-helix structure and other biological properties that mimic collagen of natural origin, enabling reliable interaction with cells and tissues and allowing easy absorption or remodelling by the human body. Evonik will use its established fermentation process technologies and global manufacturing network to commercialize the collagen platform for worldwide use. The platform will also support the company’s Tissue Engineering Project House launched in Singapore in 2018 by Evonik's strategic innovation unit Creavis to develop advanced biomaterials solutions in regenerative medicine.

Nouryon reports further growth in profitability in 2019

Specialty chemicals company Nouryon has reported further growth in profits in its full-year 2019 financial results, with adjusted EBITDA performance and operational improvement initiatives along with over Cost discipline and operational improvement initiatives leading to $110 million in improved performance of EBITDA performance and operational improvement initiatives. The company said its improved adjusted EBITDA performance and strong cash position helped support the company’s efforts in its early voluntary debt repayment of $110 million (about €110 million) in the fourth quarter.

New manufacturing equipment investments at WeyChem Lamotte

The WeyChem Group of Companies has announced an investment of €5 million in its Specialty Chemicals Assets at its WeyChem Lamotte site in France to include upgrades of filters as well as the implementation of robotic elements for improved flexibility and cost-effectiveness. After receiving approval for the investment by the Group’s owners, International Chemical Investor Group (ICIG), WeyChem will now start upgrading the site’s facilities and equipment, with plans to install an acid-proof filter dryer, expanding the site’s capabilities towards isolation of high-value chemicals as solids. In addition, a distillation toolbox for temperature-sensitive processes will be expanded by adding a stainless steel thin film evaporator, while additions to the existing manufacturing equipment will include stainless steel reactors to create a robust process pipeline. The expanded facility will also include a fully automatic solids filling and packaging line, as well as automated cleaning systems for its new production plants.
Chemours inaugurates The Chemours Discovery Hub on University of Delaware campus

The Chemours Company, a global chemistry company specializing in fluoroproducts, chemical solutions and titanium technologies, has formally inaugurated its new innovation center, The Chemours Discovery Hub, on the University of Delaware’s Science, Technology and Advanced Research (STAR) Campus. The state-of-the-art facility now houses more than 300 of the company’s researchers and scientists, consolidating most of the company’s U.S. Innovation efforts into one location. The Chemours Discovery Hub is 312,000 square feet in area, contains more than 130 individual laboratories and was built in 24 months.

At the Discovery Hub, Chemours will deepen its research partnership with the University of Delaware and perform experiments alongside professors and students to develop new applications for its products. Additionally, the company will use its facility to attract and recruit potential interns, co-ops and employees.

“This is about so much more than a new R&D facility; it’s about our company’s investment in young minds who will be introduced to chemistry at the Discovery Hub, our continued investment in Delaware, and our investment in an innovation pipeline that will empower our customers,” said Mark Vergnano, president and chief executive officer of Chemours. “When we broke ground on the Chemours Discovery Hub here on the STAR Campus two years ago, we expressed our shared vision of a state-of-the-art research partnership that would expand the boundaries of scientific knowledge, inspire the important work of our talented people, and fuel our economy for years to come,” said UD President Dennis Assanis. “Today, we see that vision becoming a reality.”

BASF wants to promote more women in leadership positions

BASF wants to increase the proportion of women in its leadership positions to 30 per cent worldwide by 2030. At the end of 2019, the proportion of female managers was 23 per cent. In 2019, BASF had set itself the target of increasing the proportion of women in leadership roles to 22 to 24 per cent as of 2021, which it achieved ahead of schedule at the end of 2019.

The company wants its goal of a better gender balance in its leadership team to be achieved for the BASF Group worldwide and for its leadership levels overall, including management levels in all countries where the company operates. The company has put special focus on the three leadership levels below the Board of Executive Directors, where the proportion of female leaders was 15.8 per cent as of December 31, 2019.

“We want to better incorporate women and their abilities in the leadership team of BASF,” said Dr Martin Brudermüller, Chairman of the Board of Executive Directors of BASF SE. “As a research-driven company, we know the value of diverse ways of thinking and working. Different perspectives result in innovative ideas and solutions for our customers.”

BASF also wants to achieve the early recognition, nomination and development of talented female employees as well as long-term succession planning, which BASF says will contribute to reaching the goal. The majority of leadership positions at BASF are filled internally, the company supporting young leaders by offering individualized mentoring and training programmes.

Gyrolab technology to be incorporated into Jefferson Institute for Bioprocessing specialized teaching curriculum and training programmes

The Gyrolab® ePhore immunoassay system from Gyros Protein Technologies is to be integrated into the curriculum at the Jefferson Institute for Bioprocessing (JIB) at Thomas Jefferson University. JIB’s industry training programmes will also benefit from the technology to accelerate the generation of biologics for preclinical development. Students at JIB will get hands-on experience with the Gyrolab immunassy system and the technology to use kits to gain enhanced industry skills, working with cutting-edge technologies that streamline and advance biologics development.

The collaboration forms part of Laverigne’s wider mission to create new uses for plastic, in this case polyolefinic teraphthalate (PET), recycled from ocean-bound waste streams. The term ‘ocean-bound plastic’ (OBP) refers to plastic waste that is recovered from the more than eight million tonnes of plastic currently entering the oceans each year. The first new flame retardant compound, Laverigne VYPET OBP FR, has 30% glass fibre reinforcement and UL 94 V-0 flame rating at 0.6 mm thickness, which makes it suitable for many electric and electronic (E&E) applications, including both aesthetic and structural parts. This fully recyclable OBP-based compound has already successfully passed moulding trials at part manufacturers and is now commercially available.

In addition, Clariant’s halogen-free Exolit OP flame retardants have been confirmed as suitable for various recycling processes without losing their flame retardant properties. Furthermore, as a contribution to reducing fossil-fuel consumption, Clariant announced in October of last year that selected Exolit OP grades will also become available as ‘feara’ types, based on renewable carbon sources.

Coronavirus: Hard surface disinfection even more crucial for food industry

UK food and beverage hygiene solutions company Christyans Food Hygiene has stressed the importance of reducing the risks of contamination from hard surfaces as combating Coronavirus continues to be top priority throughout the food chain. As Covid-19 novel Coronavirus cases are increasing and further research into the virus is conducted, evidence is emerging that infection on hard surfaces can remain for up to several days under certain conditions. Currently, there have not been any specific tests against formulated products with regard to Covid-19, however research published in Medical News Today has indicated that an oxidizing disinfectant is the most effective. The research demonstrates that solutions of hypochlorite, peracetic acid (PA) or hydrogen peroxide are particularly effective, as these solutions contain more than 65% alcohol, for example the use of a hydrogen peroxide solution such as Safest's Hawaiian TRS has proven virucidal efficacy against encapsulated viruses, and bactericidal and fungicidal activity. The product can also be used prior to the processing of organic approved products and no PPE is required and has a shelf life of up to two years.

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Exothera will aim to help cell and gene therapy innovators accelerate the delivery of their groundbreaking therapies with significant reductions in time to market and cost by taking a holistic approach to rapidly deliver scalable bioprocessing production, with initial activities in Exothera’s established facilities in Gosselies and Nivelles, Belgium and later at a 15,000 sq m site in Jumet, Belgium, recently acquired by Exothera.

The existing infrastructure of the Jumet site will be revamped to accommodate state-of-the-art laboratories, cleanrooms, and GMP-qualified manufacturing areas for clinical and commercial production. The flexible GMP areas at Jumet will contain Exothera’s CDMO activities and ongoing Univercells vaccine development and manufacturing initiatives, with capacity for rapid response programmes. Currently, the company is pursuing supporting opportunities for COVID-19 vaccine innovators.

Solvay launches Solvay One Plant sustainability programme

Industrial chemicals group Solvay has launched a new 2030 sustainability programme, Solvay One Planet which outlines ten ambitious targets to drive progress across three key pillars of sustainability: climate, resources and better life. To meet these goals, Solvay pledges to reallocate investments to promote sustainability within its portfolio, operations and workplace.

“With Solvay One Planet, we are setting bold objectives to solve key environmental and societal challenges through science and innovation,” stated Solvay CEO Edouard Claudel. “Beyond our carbon charge, we will tackle resource scarcity and promote a better life. Together with our customers, we will create sustainable shared value for all.”

Solvay One Planet is inspired by the United Nations Sustainable Development Goals (SDGs). Its ten measurable commitments in the three key focus areas, to be achieved by 2030, are:

- Climate: 1. Lowering greenhouse gas emissions worldwide.
- 2. Eliminating the use of coal.
- 3. Reducing pressure on biodiversity.
- 4. Increasing water use efficiency.
- 5. Accelerating the circular economy.
- 6. Increasing waste recycling.
- 7. Leveraging innovation to grow sustainable solutions.
- 9. Embedding inclusion and diversity.
- 10. Extending maternity and paternity leave.

Furthermore, Solvay is also taking actions internally in the three focus areas: Climate: Solvay will start switching to electric or hybrid company cars as of 2021. Resources: A new “Stop Office Waste” plan includes phasing out single-use plastic, generating almost zero food waste at canteens, and aiming to become a paperless company. Better life: Solvay is establishing a “Better Life Observatory” with managerial training to support work-life integration.

Univercells launches Exothera cell and gene therapy CDMO

Univercells has established a new cell and gene therapy CDMO business, Exothera, to provide process development and viral vector production services for cell and gene therapy innovators. The company said that the CDMO had been created to help alleviate the two most critical challenges manufacturers face in bringing these vital therapeutics to market, a structural lack of capacity and scarcity of bioprocessing expertise, and that Exothera is positioned to create bespoke bioproduction support programmes for manufacturers to achieve successful market entry.

Univercells’ novel manufacturing platforms will be leveraged, among others, to design high-quality, cost-effective viral vector processes with the option of implementing sustainable commercial facilities the customer site if desired. Exothera will aim to help cell and gene therapy innovators accelerate the delivery of these groundbreaking therapies with significant reductions in time to market and cost by taking a holistic approach to rapidly deliver scalable bioprocessing production, with initial activities in Univercells’ established facilities in Gosselies and Nivelles, Belgium and later at a 15,000 sq m site in Jumet, Belgium, recently acquired by Univercells.

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Bora Pharmaceuicals has also promoted Tim Haggerty to the position of Vice President, Global Business Development and Marketing, and prior to that, as Global General Manager, Energy Solutions, focused on Albermarle’s high-growth bromine businesses serving the oilfield and water treatment markets, among others. D’Oeyer holds a BS in Chemical Engineering from the University of Louisiana and a PhD in Chemical Engineering from Texas A & M University, as well as AQA Certification in Finance and Accounting.

Solvency has launched A new 2030 sustainability programme, Solvay One Planet which outlines ten ambitious targets to drive progress across three key pillars of sustainability: climate, resources and better life. To meet these goals, Solvay pledges to reallocate investments to promote sustainability within its portfolio, operations and workplace.

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Pfizer and BioNTech to jointly develop coronavirus vaccine

Pfizer and BioNTech SE have formed an alliance to co-develop and distribute worldwide, apart from in China, a potential mRNA-based coronavirus vaccine aimed at preventing COVID-19 infection. The companies have executed a Material Transfer and Collaboration Agreement to enable them to start working together immediately. The collaboration aims to accelerate development of BioNTech’s potential first-in-class COVID-19 mRNA vaccine programme, BNT162, which is expected to enter clinical testing by the end of April 2020. The programme builds on the research and development collaboration into which Pfizer and BioNTech entered in 2018 to develop mRNA-based vaccines for prevention of influenza. The companies expect to utilize multiple research and development sites from both companies, including in the US and Germany, to house the activities identified by the agreement. Pfizer and BioNTech will begin collaborating immediately. They will finalize details of the agreement regarding financial terms, and all activities related to development, manufacturing and potential commercialization over the next few weeks. The follow-up agreement by Pfizer on March 13 of a five-point plan calling on the biopharmaceutical industry to join the company in committing to unprecedented collaboration to combat COVID-19.

Sanofi plans to create new European APIs company

Pharmaceutical giant Sanofi is planning to create a major leading European company dedicated to the production and marketing of active pharmaceutical ingredients (APIs). The project consists of creating a standalone company that would combine Sanofi’s API commercial and development activities with six of its European API production sites: Brindisi, Italy; Frankfurt Chemistry, Germany; Haverhill, UK; St Aubin les Elbeuf, France; Opfikon, Switzerland; and Verrières, France. Sanofi said that with increasing medicine shortages critically impacting patient care, the new entity would contribute to supporting and securing API manufacturing as well as supply capacities for Europe and beyond. In Europe, the new API industry supplier is expected to help in balancing the industry’s heavy reliance on API sourcing from the Asian region. The new company would rank as the world’s second largest API company with about $1 billion in expected sales by 2022, is expected to include 3,100 skilled employee, and to be headquartered in France. A planned IPO on Euronext Paris would be evaluated with a decision expected by 2022, subject to market conditions.

People on the Move

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MFG Chemical has also promoted Tim Haggerty to the position of Vice President, Oil and Gas, where, in addition to driving topline sales growth, he will shape the company’s Oil and Gas SBU strategy, optimizing the product portfolio and developing a robust pipeline. Haggerty will work out of MFG Chemical’s new sales office in Houston, Texas, USA. Haggerty has 34 years of experience in business development with both upstream and downstream oil & gas specialty chemicals, working for such leading companies as Nalco Chemical, Sherwin-Williams Chemicals and before joining MFG Chemical in 2017. He holds a BS in Petroleum Engineering from Mississippi State University and is a lifelong Member of the Society of Petroleum Engineers (SPE) and the American Association of Drilling Engineers. Global industrial and food-grade synthetic lubricants producer and distributor ANDEPOL has appointed Maurice Sonntag as Global Sales Manager. Based at the company’s headquarters in Venlo, The Netherlands, Sonntag will be responsible for the development of the company’s sales strategy for its global network of export lubricant distributors, as well as the original equipment manufacturer (OEM) market in Europe. Sonntag has a strong track record in sales, having worked for various multinational organizations in the chemicals and food sectors. Prior to joining ANDEPOL, he spent three years at Synerlogic. He holds a Masters Degree in Sales and Accountancy.

Catalent has appointed Ricci Whitlow as President, Clinical Supply Services, succeeding Paul Hegwood, who, following a period of transition, plans to retire in March 2020 after a career of almost 45 years in operations, business development, and engineering roles. Whitlow will report to Alessandro Messali, the company’s President and Chief Operating Officer and will have global responsibility for all aspects of Catalent’s clinical supply business. Whitlow has more than 25 years’ experience in commercial, operations, and general management roles within the pharmaceutical biologics and medical device industry, and resides Catalent after two-and-a-half years, having previously held the position of VP Operations, overseeing nine manufacturing facilities across North and South America. Her most recent position was with Optheos, where she served as Senior Vice President of Technical and Corporate Operations, and she also worked for LifeCell and Johnson & Johnson during her career. She holds a Master’s Degree in Business Administration from the TRIUM programme of NYU Stern School of Business, London School of Economics and HEC Paris; as well as a Bachelor of Science in Industrial Engineering from Texas A&M University. She is also a certified Six Sigma green belt.

Bora Pharmaceuticals to acquire GSK Mississauga facility

Bora Pharmaceuticals Co., Ltd is to acquire GSK’s Mississauga, Ontario facility in Canada. The facility produces about 50 different products for more than 100 markets worldwide and employs about 450 skilled manufacturing staff who will be invited to join Bora Pharmaceuticals as part of the transaction. Bora Pharmaceuticals will continue to manufacture, under contract, the existing GSK product line for a minimum of five years.

Subject to the appropriate regulatory clearances, the transaction will see the ownership of the entire GSK Mississauga site, including all facilities, transfer to Bora Pharmaceuticals. GSK employees in the Pharmaceuticals and Consumer Healthcare commercial businesses who currently work in office space at the Mississauga site will move to new locations within an agreed timeframe following the close of the transaction. Through this acquisition, Bora Pharmaceuticals become a major global supplier of formulation development and manufacturing services and broaden its range of dosage forms, technical capabilities and geographical locations. The facility acquisition will also enable the multinational contract service provider to locally support its core markets of North America and Asia. The company currently employs more than 675 people across its two-state-of-the-art facilities in Taiwan and supplies more than 17 countries across the world, including the USA and the UK.
Enhancing drug efficacy using sustained-release coatings

The sustained-release coatings market is projected to grow from $478 million in 2019 to $660 million by 2024, a CAGR of 6.6% during this forecast period, driven by the adoption of dietary supplements, healthy lifestyles and disease prevention among consumers.

A sustained-release coating is used to form a microcapsule, which consists of active material in the internal phase, surrounded by a coating. The internal phase is called the core and the outer coating is called the shell. The diameter of the microcapsule may range from several microns to 1 mm and the shell acts as a protector or controller of the activity of the core material. The market for sustained-release coatings is growing globally at a significant rate due to their numerous applications and multiple advantages over other technologies. Some of the significant benefits of sustained-release coatings are the protection of the core material from various environmental conditions, flow control of active ingredients, targeting of specific actions, and masking characteristics.

The various active materials that are formulated into microcapsules include drugs, biosimilars, enzymes, vitamins, and catalysts, among others. These are encapsulated in many polymeric materials, including ethyl- and methylcellulose, polyvinyl and cellulose acetate, methacrylic acid, and polyethylene glycol (PEG).

North America accounted for a significant market share of 36% in 2019, followed by Europe, with a share of 28% of the overall market. The US dominated the global sustained-release coatings market with a share of 80% of the North American market in 2019. Several factors, including the increase in the production of generics, growth in the adoption of dietary supplements, rise in per capita pharmaceutical spending, and the ageing population, along with the rising incidence of chronic diseases, support market growth in the US, while the strong presence of pharmaceutical manufacturing companies in the US also makes North America a dominant market for sustained-release coatings.

**In-vitro application set to dominate**

Continuous innovation in the area of sustained-release coating designs for core phase materials drive the growth of this market. The core materials are encapsulated to prevent active ingredients undergoing various reactions or protect them from damage caused by environmental factors, such as light, moisture, pH, temperature, and oxygen. Core materials are also microencapsulated to improve shelf life and for the controlled release of active ingredients. There are two main applications areas for sustained release coatings — in vitro and in vivo research and usage.

In vitro application is the area where all therapeutic research happens outside the human body and is the domain of pharmaceutical companies, government laboratories, contract research organizations, and many private research organizations. Ethyl- and methylcellulose and PEG are the primary polymer type materials used in in-vitro applications, and for many disease conditions, a sustained-release coating is used in such applications, for example, in hormone therapy. Ethylcellulose is used for encapsulating therapeutics such as Tiotropium acetate poly (caprolactone) nanoparticles, while methylcellulose is used for encapsulating Verapamil hydrochloride based therapeutics.

**Development of mini-tablets a key trend**

Sustained-release coating facilitates better-controlled release and targeted delivery compared to the use of electrical and molecular tagging and sensors. This is an emerging market with significant potential. However, regulatory approval remains a considerable challenge for this market. The opportunity for growth mainly lies in the development of advanced sustained-release coating systems for targeted delivery of difficult-to-use ingredients and for formulating pharmaceuticals as tablets and capsules. Tablets are the most frequently used form of solid oral dosage. They are made up of multiple substances, including active drugs, which cause it to break down rapidly when moistened. Tablets are hard and compressed drugs with or without a coating, further segmented into chewing tablets and lozenges. These substantial oral dosages disintegrate in the mouth in the presence of saliva. They are usually used for local and systematic effects and are also more chemically stable, convenient, and safer than most other dosage forms. Tablets differ from each other in terms of size and weight, depending on the drug.

The development of mini-tablets is a key trend in this market segment. This type of tablet has garnered considerable attention due to its advantages — no need...
for solvents during production, ease of manufacturing, less coating material required, less risk of dose dumping, and less inter- and intra-subject variability. Versatile sustained release, immediate-release tablet systems, modified-release tablet formulations, and excipient technologies are other advances driving this market.

Advanced technologies to tap into niche markets

With the increasing demand for microencapsulated products, significant R&D activities are being carried out by various companies in this market sector. New technologies are needed to tap into niche markets, such as the use of Phase Change Materials (PCMs) in energy applications, cancer and brain tumour-specific drug delivery. Market players in PCMs are working on new product development, sustained release coating technologies, enhancements to latent heat storage capacity, and the evaluation of different phase change temperature options for enhancing product performance. However, there are no technologies available for the use of microencapsulated PCMs above 932°F (500°C), as required by the energy sector, and addressing this need is expected to provide further market opportunities. According to the WHO, tumour and cancer incidences globally are estimated to increase to 15 million by 2020. The World Cancer Report also shows that cancer and tumours are spreading at an alarming rate worldwide. This issue needs to be addressed with the help of an efficient drug delivery system. Presently, there is a lack of targeted drug delivery technologies that deliver therapeutics to the location of a brain tumour as crossing the blood-brain and brain-tumour barriers to achieve high drug concentration at the tumour site is a major challenge for targeted drug deliveries. Current therapies in this area are based on the local controlled delivery of anti-cancer agents through biodegradable polymers. Thus, the need for more advanced targeted delivery therapies, especially for the treatment of brain tumours, offers an excellent opportunity for the growth of the global sustained-release coatings market.

Reference


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The market also offers opportunities for the development of technologies for products used for animal care, which is expected to have significant scope in the future, while in the pharmaceutical industry, there is a limited presence of organ-specific drugs and the development of these drugs would also provide a significant market opportunity. Furthermore, the market offers opportunities in terms of reducing capsule size, increasing bioavailability, and providing multi-component delivery systems.

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Figure 1. Sustained-release coatings market by region, 2019.

Figure 2. Sustained-release coatings market by application, 2019

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Pharmaceutical quality: concepts, misconceptions, realities and remedies

Pharmaceutical companies have a moral and ethical obligation to ensure that their products meet regulatory standards and are therefore fit for human consumption. But in reality, the quality of any given pharmaceutical often shows too great a variation which ultimately puts patients at risk. In this article, Girish Malhotra, President of EPCOT International, explores how API quality can be greatly improved by the adoption of continuous manufacturing and how regulatory bodies can ensure high product quality with stronger punishments for non-compliant players.

Pharmaceutical quality, especially for generic drugs, has been going through its cyclical ups and downs. Discussion heats up and then goes dormant until the next major quality issue appears. One would expect that every pharma manufacturer (API and their formulator) would be on their toes and prevent regulators from issuing 483s or equivalent citations and prevent news reports from writing about out-of-compliance issues. Unfortunately, oversight at companies keep occurring and the press is forced to report to this.

For most of us, product quality reflects a company’s integrity, intelligence, knowledge and ability to manufacture products that are the best in their class. The irony is that the cost incurred to achieve first-time quality is very low or nothing if done right the first time. Properly designed and executed manufacturing processes are supposed to deliver quality products. Recurrence of quality issues (deviation from established specifications, lack of data integrity and cGMP practices), especially in pharma have a common theme. They are a reflection of a shortfalls in the company’s integrity, management, knowledge and manufacturing practices. Every oversight can result in an issue.

It is critical to understand pharma’s manufacturing landscape as it affects product quality. Every company knows what is needed, but the ultimate question is ‘do they produce repeatable quality products that meets established specs using cGMP practices?’

Financial model

Companies have to follow a criterion that gives companies an advantage over their competitors, whether it pays them to be in the business. As explained below, too many API producers and formulators could also be part of current quality variation problems.

Batch vs continuous process

Improved quality is being touted as one of the benefits of using continuous processes rather than batch. This is true if there is such a process for the manufacture of APIs and their formulations which would produce the same product for about 7,500 hours per year. However, volume is needed to have a steady run from the same equipment. If the process is stop and go, it is no different from any batch process. In addition, significant understanding of the chemistry involved, component interaction and execution control is needed. This can present formidable and different challenges for manufacturing APIs and their formulations. If all were easy, then continuous manufacturing, especially for formulations, would have been adopted in pharma manufacturing 60+ years ago.

Drug dose and product demand determine API and formulation needs. Table 1 illustrates API and tablets needed to satisfy the needs of 50 million patients per year. For decades of economics and chemical engineering were applied, the most likely needed API (dose 1 milligram) could be produced in a single plant. Pharmaceutical API could also be done at a single plant requiring multiple parallel formulation lines operating year-round. For a 50 milligram dose, a single plant using a continuous process would be sufficient to meet the global API needs. But reality multiple plants are used to produce the API and their formulations. This is an extremely important point, as quality from each API and their formulations) facility can vary even if every plant were an exact replica of each of the others. This is due to a myriad of factors (people, raw materials, equipment and even execution).

Table 2 is an illustration of the reality for some of widely used drugs. Process economics should dictate process selection but that is not the reality and the fundamentals of engineering and economics are not applied in manufacturing process selection. It is interesting to note that Pfizer produces 250 tonne continuous API at three sites but now it is being produced at 44 sites and is being formulated at over 800 sites (by different companies). Every product will not be exactly the same. We can all draw our own conclusions about batch-to-batch variations as it shows too great a variation, which ultimately puts patients at risk. Another interesting fact we have to recognize is that the FDA or any other regulatory body does not have adequate manpower to do even risk-based inspections just for these six drugs.

Current APIs and their processes

If done right the first time. Properly designed and executed manufacturing processes are supposed to deliver quality products. Recurrence of quality issues (deviation from established specifications, lack of data integrity and cGMP practices), especially in pharma have a common theme. They are a reflection of a shortfalls in the company’s integrity, management, knowledge and manufacturing practices. Every oversight can result in an issue.

Companies have to follow a criterion that gives companies an advantage over their competitors, whether it pays them to be in the business. As explained below, too many API producers and formulators could also be part of current quality variation problems.

Table 1. Theoretical API and formulation needs

<table>
<thead>
<tr>
<th>Patients</th>
<th>Number of days per year</th>
<th>API, kilo per year</th>
<th>Tablets, kilo per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>50,000,000</td>
<td>365</td>
<td>18,250</td>
<td>12,500</td>
</tr>
<tr>
<td>50,000,000</td>
<td>50</td>
<td>18,250,000,000</td>
<td>12,500,000,000</td>
</tr>
</tbody>
</table>

Table 2. Number of sites for APIs and formulations.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of API sites</th>
<th>Number of FDD sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>22</td>
<td>536</td>
</tr>
<tr>
<td>Atorvastatin calcium</td>
<td>44</td>
<td>865</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>87</td>
<td>768</td>
</tr>
<tr>
<td>Modafinil</td>
<td>29</td>
<td>70</td>
</tr>
<tr>
<td>Metformin HCl</td>
<td>77</td>
<td>752</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>300</td>
<td>3,329</td>
</tr>
</tbody>
</table>

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Overcoming the challenges of phyto-API supply

Phytochemical active pharmaceutical ingredients (APIs) come from plants, and each has unique properties and considerations for pharmacological use in humans. C² PHARMA manufactures and distributes niche phytochemical and ophthalmic APIs with a focus on sustainable and reliable supply chains: this article gives an overview of the supply of digoxin.

Natural and synthetic phytochemical considerations

Plants contain complex chemical substances that impart unique properties, such as resistance to attack by microbes and other predators. Many of these compounds are also pharmacologically active in humans, providing significant therapeutic effects. Indeed, many important APIs, such as the anti-cancer drug taxol, were originally isolated from plants.

In some cases, such as for taxol, despite the complex structures of these small molecules, synthetic routes have been developed to manufacture them reliably. For others, however, synthesis is not practical.

The digoxin example

The heart disease treatment digoxin (a long series of saccharides with a wide range of functional groups), which is on the WHO essential medicines list, cannot be synthesized economically. This makes securing the supply chain challenging because phytochemical concentrations in plants are highly influenced by growing conditions such as soil nutrients, temperature and moisture/humidity. Plants grown in different geographic locations on plantations that use diverse fertilization practices will have variable compositions of phytochemicals and if there are extended periods of unusual weather conditions such as excessive drought or rain, there can be a large impact on the level of the phyto-API and similar compounds in the plant.

Siting plantations in locations with ideal growing conditions and implementing good agricultural and collection practices (GACP) can help increase the production of the desired phyto-API. The timing of the harvest also affects the phyto-API and other compound content from batch to batch of plant material. Many batches are required because the concentrations of phyto-APIs in plants tend to be relatively low, requiring large amounts of dried plant material to produce measurable quantities of purified API.

Furthermore, extraction of the desired compound from dried plant material is often just the first step in the production of natural-product APIs. In most cases, the desired compound is obtained along with numerous other phytochemicals, many of which have very similar structures. For a low-concentration phyto-API like digoxin, the concentration may be similar to that of the other compounds present in the extracted mixture.

Concentration synergies

Within one plant, there can be multiple phytochemicals with a synergistic effect that results in more potent extracts. These structural analogues are considered when designing extraction and purification processes, as is elimination of any phytochemicals that do not have a positive impact on the effectiveness of the end phyto-API. The need to retain select structural analogues and separate others can be complicated.

Due to its high toxicity, digoxin also poses additional problems, and its production requires highly specialized expertise. Separation and purification are achieved via a series of extraction, concentration and recrystallization steps.

Manufacturing process parameters are also essential throughout each step of extracting and purifying digoxin to ensure maximum yields and quality and minimum variability. Final processing is crucial, as the appropriate particle size distribution must be achieved to ensure that each micro-dosed tablet of digoxin will dissolve evenly in the stomach.

Partnering for redundancy and reliability

In the past, shortages of digoxin occurred regularly due to a lack of focus by the incumbent manufacturer on both the manufacturing technology and on the reliability of supply of the Digitalis lanata plant. Depending on the severity, a shortage could mean life-threatening consequences for patients that rely on digoxin.

C² PHARMA has invested in both digoxin manufacturing and the planting of Digitalis lanata to create a redundant supply chain to overcome any risk of shortage. The plant is grown across various locations in Europe adhering to stringent GACP regulations and a dedicated state-of-the-art drying facility has been built to handle optimal drying of the leaves. In parallel, a programme with one of Germany’s leading universities has been pursued to continue breeding more productive varieties of Digitalis lanata.

A cutting-edge production facility was established in Vizag, India and is operated by contract manufacturing partner Launus Labs. An alternative digoxin product portfolio manufactured at a production facility in Poland was acquired from Mobilitis Ent., which inherited its own digoxin manufacturing technology from Roche/Galenus Mannheim; and the company remains a manufacturing partner and distributor for this API.

C² PHARMA also partners with logistics experts for the handling of highly potent APIs and temperature-sensitive products, such as digoxin.

Both the Indian and European manufacturing sites for C² PHARMA’s digoxin API have been audited by regulatory authorities in the US, Europe, and Asia. While there are slight differences in impurity profiles in the digoxin products produced in India and Poland, both meet US and European Pharmacopeia specifications.

Access to two sources of digoxin API with separate supply chains for the Digitalis lanata leaves enables C² PHARMA to ensure a unique and redundant supply for this API.

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Grand Challenge 1: opportunities for partnership and investment

Dr John Robertson, Senior Research Fellow at the University of Strathclyde, describes how the ‘Grand Challenge 1’ project being run by the Medicines Manufacturing Innovation Centre, a collaboration between the Centre for Process Innovation (CPI), UK Research and Innovation, Scottish Enterprise, and founding industry partners, AstraZeneca and GSK, is working on new pharmaceutical process technologies to meet the real need to reduce the costs of drug development.

A rapidly ageing population and the eye-watering cost of drug development are placing the pharmaceutical and health care sectors under unprecedented strain. There is a critical need to reduce R&D expenditure while also improving the ways in which health care systems provide treatment to the growing proportion of elderly patients. This is a highly complex challenge to overcome and part of the solution involves fundamentally changing the way that pharmaceutical manufacturing currently operates.

Traditional batch manufacturing processes often require long optimization times and are not flexible enough to respond to fluctuating drug demand or to deliver personalized medicines. However, developing new and future-proofed solutions requires investment and expertise not available within any one government, organization or private company. Instead, representatives of the entire value chain must come together to work as part of bold new models for partnership and investment, which is the remit under which CPI’s Medicines Manufacturing Innovation Centre was founded. The centre, based in Renfrewshire, UK, is bringing together government, academia and industry to develop agile technology platforms. This will eliminate inefficiencies in the pharmaceutical supply chain and lower the cost of drug development.

The Medicines Manufacturing Innovation Centre’s founding industry partners, AstraZeneca and GSK, are two of the UK’s leading pharma companies and this is the first time they have combined their expertise to co-develop new technology. The centre is also receiving valuable input from its academic partner, the University of Strathclyde, as well as a host of SMEs from across the supply chain as part of the Medicines Manufacturing Innovation Partnership (MMIP). Funding support is being provided by Scottish Enterprise and UK Research and Innovation. Although the future of pharma manufacturing will be challenging, ambitious projects at the new centre such as Grand Challenge 1 are demonstrating the tremendous opportunities on offer for those bold enough to get involved.

This time it’s personal

Grand Challenge 1 is one of the Medicines Manufacturing Innovation Centre’s flagship projects and aims to improve current production methods for oral solid drug formulations. Inefficient and inflexible manufacture of solid drugs was a key issue identified after extensive consultation with companies across the pharmaceutical supply chain. The collaboration at CPI’s new centre will solve this by developing a digitally-twinned continuous direct compression (CDC) manufacturing platform. CDC provides fine process control compared with batch methods, enabling the scalable and rapid production of the highly tailored drug formulations that are required for simple, cost-effective, agile manufacturing processes.

The project is well underway, with the CDC platform’s digital twin currently being developed at the University of Strathclyde. This is a key innovation, as it will enable pharmaceutical manufacturers to optimize their formulations in digital space, drastically reducing the time and raw materials required during this process. The expertise offered by the University of Strathclyde within the realms of pharmaceutical manufacture and characterization has been crucial in making this ambitious project a success. In addition, the centre’s industry partners are contributing their extensive knowledge of pharmaceutical manufacturing and are helping to establish the business case for this new technology and, once completed, Grand Challenge 1 will offer an open-access platform for companies developing new formulations.

Successful collaboration relies upon every partner having the opportunity to make its voice heard and the support to meet its unique objectives. This requires strong and open communication between partners, exhibiting levels of transparency not often seen within the industry. The involvement of two competitors with highly disjointed expertise in Grand Challenge 1, AstraZeneca and GSK, makes honest communication even more important, but the value it is adding to both companies makes this radical model of collaboration well worth the effort.

From challenge to opportunity

A recent workshop held at the University of Strathclyde with industry experts, equipment suppliers, government and academia mapped out the future of the Medicines Manufacturing Innovation Centre. Key issues in the pharmaceutical supply chain were identified and a shortlist of proposals for future grand challenges was created. This included a clinical direct compression platform as well as a platform for particle design and delivery.
Nanoforming: the new revolution

Sally Langa, Head of US Sales at Nanoform, describes how the latest nanoparticle engineering technology promises to improve efficiency in the pharmaceutical industry.

Bringing a new drug to market is a monumental task, involving the combined efforts of scientists across all disciplines and development pipeline. The entire process can often take 12-15 years, and the development of a single drug often comes with a price tag of over $1 billion. [1] Considering the life-changing benefits that new medicines can bring to patients globally, this is not such a high price – a bigger problem arises from the low success rates associated with drug development. For example, while $182 billion was poured into R&D in 2019 alone, only 48 drugs were approved for use.[2-3] This is far from an anomaly – from 2010 through to 2019, the FDA has averaged approval of just 37 novel drugs per year, despite ever-increasing funding. Moreover, the likelihood of success for a compound entering Phase 1 trials is slight under 10 per cent. This is significant: no other major business type operates under such a high failure rate.[4]

With the incredible expense and low success rates associated with drug development, there is a shared feeling in the pharmaceutical industry that technological innovations are greatly needed to improve efficiency. Nanoforming, the process of engineering drug compounds into nanoparticles, has emerged as one such innovative technology.

The problem of poor solubility and bioavailability

Major causes of attrition in pharma are issues arising from low bioavailability and solubility of drugs,[5] if a drug cannot reach its target area, no matter how promising its pharmacodynamic properties in vitro, it will fail in clinical trials.

The solubility of a compound defines its ability to dissolve in a solvent to produce a homogenous solution. A drug’s bioavailability, meanwhile, refers to the extent and rate at which the drug enters systemic circulation in an unchanged form, thereby reaching its target area. A large proportion of drugs is administered orally and absorbed into the body through the gastrointestinal tract. Poorly or even nonexistent solubility and poor water solubility will result in poor drug absorption through the intestinal wall, negatively impacting bioavailability.[6] With more than 40 per cent of new chemical entities (NCEs) developed in the pharmaceutical industry almost entirely insoluble in water, this is a major problem for formulation chemists.[7] A further issue is the increasing complexity of drug compounds, resulting in higher molecular weights and increased hydrophobicity. These characteristics decrease drug solubility, complicating drug development. As the trend towards more complex drug compounds further establishes itself in pharma, it is expected that the emphasis on finding new ways to improve drug solubility and bioavailability will continue to grow.[5]

Current technologies addressing the issue

There are a number of technologies on the market today that strive to address the issue of poor bioavailability and solubility of drug candidates. One of the most frequently used techniques is that of spray-drying formulations of amorphous solid dispersions. While effective, the technique can produce amorphous material and make it challenging to form tablets or capsules. Nanomilling, meanwhile, is an example of a top-down approach by which particle size is reduced through milling in a wet medium. It can successfully produce nanoparticles as small as 10nm, albeit with varying mechanical stress the technique can also create amorphous domains, causing aggregation and potentially changing the polymeric form of the drug. Furthermore, while techniques such as co-crystals – in which a drug compound and water-soluble molecules are engineered to form co-crystals with water-soluble molecules – are highly effective, they may not be suitable for all drug molecules.[6]

The latest technology: nanoforming

Nanoforming, the process of engineering drug compounds into nanoparticles, has emerged as a compelling solution to the problems associated with poor drug solubility and bioavailability.[5] A drug particle sizes down to the nanoscale, nanoforming maximizes contacts with its solvent molecules, thereby improving solubility. The latest nanoforming technology, referred to as the ‘controlled expansion of supercritical solutions’ (CESS), achieves uniform nanoparticle sizes by employing a bottom-up recrystallization technique to produce crystalline materials from solution in a controlled process. The resulting particles are tunable in size, shape and polymeric form. The nanoforming process dissolves and extracts API particles from supercritical carbon dioxide (scCO₂). Without changing the API’s inherent chemical properties. Furthermore, supercritical methods offer better scalability than other nanoforming techniques and are therefore more industrially relevant.

Benefits for the pharmaceutical industry

To be transported into the deep lung, opening up new possibilities for the treatment of respiratory diseases. Nanoparticles can be inhaled from the lung due to their low inertia, therefore nanoparticle medicines are often coupled to a larger delivery framework. Particles of 1-5 microns are ideally suited to pulmonary delivery, possessing the correct aerodynamic parameters for transport into the periphery of the lung. Systemic circulation of the drug through the lung is also possible with decreased drug particle size, and an attractive option due to the rapid onset of action observed through this route.[8,9] In addition to facilitating drug delivery into and through the deep lung, nanoparticle technology also provides a compelling solution to the problems associated with poorly water-soluble molecules, improving bioavailability and helping the industry to move towards safer carbon-neutral footprints. Meanwhile, research has shown, however, that nanoparticles can be transported through channels created by hair follicles, opening up new avenues for the development of topical treatments.[13]

Lowering the dose

Studies also show that by improving the absorption of drug compounds into the body, the latest nanoforming processes can enable smaller, safer, and potentially more effective doses of medicines to be administered.

A bright future

Nanoforming has emerged as a compelling solution to the high rate of attrition and increasing complexity of drug candidates in pharmaceutical development today. The benefits it brings to the industry are manifold, from addressing a cause of drug failure by improving bioavailability and solubility to improving cost-effectiveness and creating new avenues for drug delivery. With the latest technology emerging, the pharmaceutical industry is struggling under the weight of inefficiency, the exciting implications of the technology are expected to make an important difference, providing 100 per cent success in drug development from market and doubling the number of drug candidates entering clinical trials. Moving forward, there can be no doubt that the technology will make a lasting mark.

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Nanoform scientists engaged in nanoparticle engineering research.
The billion-dollar biopharmaceutical industry shows no signs of slowing down as biologics, including vaccines and cell and gene therapies, present new promise to prevent, treat, or even cure diseases. Still, as business continues to boom, supply remains a challenge—one that Belgium-based company, Univercells, is helping to overcome with bioprocessing innovation.

The biopharmaceutical sector is now a billion-dollar industry providing prevention, treatment and sometimes even cures to severe indications. This sector is segmented in multiple product classes including vaccines and cell and gene therapies. Even though these products have a track record of proven efficiency, the global supply of these life-saving biologics faces significant challenges—one of the greatest being supply.

Supply shortages are affecting the quality of life of millions of people, as these result in failure to adequately treat patients and, in the case of vaccines, failure to meet disease eradication targets. Challenges surrounding the global supply of biopharmaceuticals differ across product classes: for example, while vaccines have been routinely manufactured and distributed since their first introduction over 200 years ago, current processes for vaccine manufacture typically rely on outdated expensive technology with low flexibility to respond to market fluctuations. On the other hand, in gene therapies, the fast growth of this sector has not allowed for technology innovation to keep up, and most manufacturing processes rely on non-scalable technologies. This poses a critical issue as products approach the later stages of the clinical trials pathway and in time, commercialization.

**Need for technical innovation**

The challenges related to the supply of biopharmaceuticals highlighted above seem to have a common root: technical innovation, as adequate technology advancements are needed to reduce footprint and enhance scalable, robust and cost-effective manufacture of biologics. In order to address the current gaps in technology availability in the biopharmaceuticals sector, Univercells has designed a next-generation platform for biotherapeutics manufacture: The NevoLine biomanufacturing platform.

This disruptive platform uses technological innovation to achieve cost-effective manufacture of biologics in a modular format. The principles of process intensification, channelling and automation are combined in self-contained modules to drastically reduce facility footprint, and capital and operational expenditures. These modules can be configured with product- and process-specific containment levels as well as number of particles per cubic meter environments, enabling bespoke solutions to customer-specific applications. The modules can be adapted and assembled to fit different process requirements and can be adjusted onsite at any point in order to facilitate multi-product manufacture.

**NevoLine platform**

The NevoLine platform is compatible with various modular configurations (surface area per sq m of area for cell growth within 2.4 m², 10 to 30 m², 200 to 600 m²). The NevoLine platform includes BioRenewable solvents from waste feedstock that avoid using non-renewable resources, as well as greener alternative solvents to replace those posing health or environmental risks. A perfect example is our award-winning Cyrene™ – a safer, bio-based alternative to DMF and NMP – made from renewable cellulose waste in an almost energy-neutral process that releases water.

Why choose between solvents that are ecological and those that are reliable? Enjoy both with high-quality, environmentally friendly alternatives. Our growing portfolio includes BioRenewable solvents, from waste feedstock that avoid using non-renewable resources, as well as greener alternative solvents to replace those posing health or environmental risks. We’re dedicated to supporting all your explorations responsibly. See how easy it is to switch to sustainable lab practices on: SigmaAldrich.com/biorenewable

**Figure 1:** Comparison between the scale-X bioreactor and traditional technologies (10-layer cell factories) for adherent cell culture where the scale-X bioreactor provides up to about 1,000-fold higher capacity per cell culture vessel.
The first application of this platform was a configuration for the manufacture of a trivalent Sabin strain inactivated poliovirus type (sIPV) vaccine using Vero cells. The work was performed under a grant from the Bill & Melinda Gates Foundation with consortium partners, Batavia Biosciences and Natrìe (Merck Millipore). Poliomyelitis (polio) is an infectious disease that can cause debilitating paralysis or death, and for which there is no effective treatment available, making prevention through immunization the best strategy to overcome it. At the start of the project, the supply gap for polio was 50 million doses.

Interconnected modules for vaccine production, purification and inactivation

The NevoLine platform consists of three interconnected modules containing selected equipment and single-use items for the production, purification and inactivation of a live polio virus vaccine. Given the biosafety level required for this application, isolators were used as modules. The interconnected modules contain the entire production sequence up to bulk drug substance preparation. In-line decontamination of liquid waste and the thermal/HVLP decontamination of solid waste take place outside the modules. The unit operations carried out within each of the three modules are:

- **Upstream (USP) module:** Cell culture in the scale-X bioreactor, infection and concentration
- **Downstream (DSP) module:** Clarification and purification
- **Inactivation (INAC) module:** Virus inactivation

The initial experimental results attained with the intensified process designed to be integrated into the NevoLine platform have demonstrated a superior performance in harvest titers and DSP yields with respect to current processes. These results, combined with the additional benefits of the design of the NevoLine platform, resulted in a COG reduction of 2 to 5-fold and a CAPEX reduction of up to 10-fold.

The high success observed in this first application resulted in Univercells receiving the CPhI Award for Excellence in Pharma: Bioprocessing & Manufacturing during CPhI Worldwide 2019 in Frankfurt, Germany last October. The team at Univercells is working on various applications of the platform, as well as concepts for other targets with the most advanced project being in gene therapy products.

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**Figure 2** The NevoLine for sIPV manufacture.

**Figure 3** Economic benefits of the NevoLine for sIPV platform.

<table>
<thead>
<tr>
<th>Impact</th>
<th>NevoLine</th>
<th>Single-Use (SU)</th>
<th>Stainless Steel (SS)</th>
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</thead>
<tbody>
<tr>
<td>&gt; 60 to 90% reductions in CAPEX</td>
<td>- 39</td>
<td>- 50</td>
<td>- 300</td>
</tr>
<tr>
<td>&gt; 62 to 85% reductions in footprint</td>
<td>- 10,000 m²</td>
<td>- 2,500 m²</td>
<td>- 2,500 m²</td>
</tr>
<tr>
<td>&gt; 85 to 93% reductions in utilities consumption</td>
<td>- 20,000 USD</td>
<td>- 20,000 USD</td>
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<tr>
<td>&gt; 53% to 81% reductions in COG</td>
<td>- $ 0.30</td>
<td>- $ 0.6</td>
<td>- $ 1.2-1.5</td>
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**Source:** Univercells

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According to the World Health Organization, there are about 60 million people with diabetes in Europe. That number is on the increase worldwide, among all age groups, largely as a result of growing levels of mostly preventable risk factors such as obesity, physical inactivity and poor dietary habits. Sugar boosts the level of glucose in the blood and causes the pancreas to release insulin. Higher insulin levels lead to the storage of dietary calories as fat, which results in weight gain and obesity – both risk factors for diabetes. This can then lead to increased risk of a number of other major health issues, including heart disease, stroke, kidney damage, cataracts and nerve damage. However, high blood sugar levels can be effectively managed if caught early. Thus, there is a growing need for health solutions targeting prediabetes.

**Plant-based solutions from Mother Nature**

While there is no doubting the severity of such health problems, the opportunity for natural solutions is growing rapidly. Phytohormones are the response of plants’ evolutionary mechanisms to survive environmental conditions. Therefore, researchers are now looking at the possible effect of dietary plant hormones on human health. For instance, abscisic acid (ABA) is naturally present in many fruits and vegetables.

Figs contain one of the highest concentrations of ABA found in nature. It is also produced in our bodies in the metabolic pathway of vitamin A, and plays an important role in managing blood glucose and inflammatory homeostasis. That is why Euromed, a leading manufacturer of therapeutic botanical extracts, has launched ABAlife—a patented extract from figs containing a standardized amount of ABA.

**Fig extract for blood sugar control**

A human study found that health conditions associated with impaired glucose tolerance correlated with lower levels of plasma ABA. These were restored after a return to normal health, showing the physiological significance of ABA on glycemic control. According to a survey of the European Union (EU) population, in 2017, only about 1 in 4 people ate fruit and vegetables at least twice a day. Thus, they may have insufficient intake of ABA and would therefore benefit from a dietary supplement containing ABAlife.

A randomized, double-blind crossover study from the University of Sydney evaluated the efficacy of Euromed’s fig extract on glucose metabolism blood parameters. It has been shown to improve glucose tolerance, assist insulin release and may help to lower post-prandial blood glucose levels. The researchers investigated the effects of two different ABA doses in fig extracts (100mg and 200mg) on post-prandial glucose and insulin responses in healthy subjects. A 200mg dose of ABAlife added to a glucose drink lowered overall blood glucose, insulin levels and peaks between 30 and 120 minutes post-dose, and significantly improved glycemic index (GI) levels compared with a reference glucose solution. The GI indicates how fast and efficiently the body can metabolize a carbohydrate meal. The lower dosage was also effective on GI but did not reach statistical significance. Both dosages, however, were able to significantly lower the post-prandial insulinemic index (II), which shows how much insulin the body releases in response to a meal. This initial study suggests that ABAlife may be a beneficial dietary supplement in terms of helping to maintain healthy blood sugar levels, and an adjunctive treatment for chronic metabolic disorders such as prediabetes and type 2 diabetes. A clinical development plan to further investigate other dosages and longer administrations of the extract in various health conditions is ongoing.

**Scientifically proven health benefits**

While we can’t change risk factors such as age, gender or genetics, we can make diet and lifestyle changes. Predominantly plant-based dietary patterns are recommended to support longevity. Following a Mediterranean-style diet – rich in polyphenols and other plant substances – and limiting sugar intake, can help in the management of diabetes and related metabolic diseases. ABAlife delivers the scientifically proven health benefits of ABA while avoiding the additional calories and glucose associated with eating figs. This could help with the development of natural medicines, functional foods and drinks that effectively support glucose metabolism.

Moreover, ABAlife would also be the perfect companion for ketogenic diets.

**References**

Creating ‘the best fit for purpose flow reactor’ by 3D metal printing

André de Vries, Commercial Director, and Raf Reintjens, Principal Scientist Process Intensification, both from InnoSyn, share their thoughts on Selective Laser Melting (SLM or “3D metal printing”) as enabling technology for the manufacturing of tailored flow reactors and mixers.

The benefits of continuous manufacturing for the chemical industry are well documented. Lately, also the small molecule pharmaceutical arena has adopted so-called flow chemistry as one of their focus points to improve manufacturing processes. The arrival of a wide range of flow reactor systems from several equipment providers has enabled a first proof of concept of flow processes for a vast variety of reactions, both in academia and pharma industry.

Typical useful chemical reactions to perform preferably in a continuous mode can be divided into two main categories. Notably, the very fast, highly exothermic reactions, such as nitrations, DiBAl-H reductions and alike, and metalorganic reactions. These are very much helped by the hugely increased heat and mass transfer of small tubular reactors compared to batch vessels. Also, the residence time distribution narrows which has an additional positive impact on the selectivity. A second class of reactions ideal for flow are the ones using a hazardous or potential explosive reagent, or reactions operating via an hazardous reaction mixture. Continuous operation is much more safe, since there is no accumulation of such a hazardous reagent and/or mixture.

The variety of reactions in both groups is enormous though, hence, a tailored piece of flow equipment would be the best solution for performing these reactions in the most productive, and safe mode. At InnoSyn we adopted SLM, or 3D metal printing, as enabling manufacturing technology to create these best fit for purpose reactors and mixers. The application of 3D metal printing grows exponentially and is driven by the aerospace, automotive and medical devices industry. SLM is capable of printing full dense objects in any metal that can be welded – gives the possibility to adjust to the corrosiveness of the reaction mixture - and it provides almost an unlimited freedom of design.

For highly exothermic reactions a large heat transfer is preferred, possibly to be obtained by 3D metal printed double jacketed flow reactor with a relatively narrow channel (up to 2 mm) and a zigzag pattern for additional secondary flow phenomena (Dean vortices), see Figure 1, upper left. If even better mixing is required and very short residence times we have developed a Y-type static mixer, see Figure 1 upper right, where diameters and flow speeds of both reagents can be altered to its needs. They exhibit excellent mixing capabilities as determined independently by MSD (OPRD, 2018, 22, 1015). When applying hazardous reagents in relative slow chemistry, for example SN2 substitutions with sodium azide at sterically hindered alkyl bromides, one would prefer to use a rather large flow reactor (250 mL shown) to reach the required residence time of multiple minutes. Key here is to achieve a narrow residence time distribution, which can be obtained using SML elements in straight pipes of ca 1 cm (figure 1 bottom).

Figure 1. Upper left: Double-jacketed 3D-metal-printed flow reactors, and a cut-open one, all with a zigzag channel for superb heat transfer (U up to 10,000 W/m2K). Upper right: Static mixer, design and a 3D-printed example. Bottom left: Design of a 250mL flow reactor with SMLX elements for relatively slow reactions. Bottom right: the 3D-metal-printed result.
Flow Chemistry

When investigating in the lab, the flow reactors and mixers with different features can be connected due to the Swagelok fittings. Once the important parameters, like which mixer to use, reaction temperature, flow speeds (residence times) etc., are set one could opt to design and 3D metal print all features in one device. For highly reactive and exothermic chemistry we designed such an all in one device (see figure 2), where there is the option to use up to 4 injection ports (double jacketed T-mixers) to control the temperature rise to its limits. As an additional feature also 5 thermo sensors (PLC) are available. When investigating in the lab, the flow consumption, making it according to us the preferred technology to manufacture the best fit for purpose flow reactors and mixers. Together with DeDietrich Process Systems a partner with an excellent reputation in the field of engineering and construction of process installations, we have recently developed a ready to roll in skid (dubbed as CryoFlowSkid, see Figure 3), ideally suited for executing highly exothermic chemistry, for example the 3-step sequence of in situ organometallic reagent preparation, it’s addition to a ketone or imine, and a subsequent quench.

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Figure 2. Design of multi-injection and multi temperature probe reactor (all double jacketed) for highly exothermic chemistry (HTF = Heat Transfer Fluid).

Figure 3. The CryoFlowSkid for highly exothermic chemistry by DeDietrich Process Systems; InnoSyn’s 3D metal printed reactors inside.

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The entire system is compact so that it can be placed in a drive-in fume cupboard. The control box is loose and can be driven away from the process part. Process control, data acquisition and safeguarding are all automated (PLC). All refrigerated components are located in an insulated chamber that is flushed with dry nitrogen to prevent ice buildup. The reactors contain several temperature sensors that measure the temperature in the reaction channels. Depending on the exact chemistry to perform, scales of up to 100 kg per day of product could be obtained with this ready to roll in skid.

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SCIENTIFIC UPDATE
We’ve got chemistry
Advantages of continuous flow synthesis

Continuous flow chemistry has, until recently, largely been a niche problem-solving technology, typically employed when a developed process presents a hurdle, such as energetic chemistries or issues with capacity that require an alternative solution. However, the technology is a powerful addition to the process toolbox, although its advantages are not yet fully appreciated. Dr Shawn Conway, Engineering R&D Director, Cambrex, describes the possibilities that it can unlock.

Batch production may be the workhorse of the pharmaceutical manufacturing sector, but the economic and technological advantages of continuous flow chemistry are encouraging many active pharmaceutical ingredient (API) manufacturers to give it serious consideration. Continuous manufacturing techniques are not new, but the pharmaceutical sector has only started to explore the possibilities that this technology offers in the past two decades. In theory, any synthetic process could be carried out in continuous mode, but in practice, good candidates for moving away from batch manufacturing will involve a relatively rapid chemical reaction of a type of chemistry that is not readily scalable using current batch processes.

Economic advantages

There are several potential major economic advantages in moving from batch production to continuous flow. First, the equipment is much smaller, which reduces the manufacturing footprint, freeing up additional processing space; and second, the smaller equipment makes key process parameters such as temperature and pH easier to control, which in turn can reduce impurity formation and improve product quality. Some drugs may be required in only small commercial quantities, either because they are highly potent or because they serve a limited patient population. Small commercial batches can be extremely expensive and inefficient to manufacture in large-scale equipment because of high infrastructure costs and the need for the same verification and cleaning procedures as large runs. A continuous process makes the use of dedicated, or even disposable equipment, for small volumes more feasible. Additional cost benefits can result from lower inputs: energy consumption and solvent usage will be reduced significantly, or in some cases eliminated entirely, as a result of enhanced control over the process. Furthermore, less waste solvent produced means lower associated disposal costs. Additionally, lower labour requirements and the need for fewer analytical procedures reduce the operating costs, and process efficiencies can increase yield and improve quality. Whereas standard commercial batch equipment can have limitations in terms of temperature or pressure capabilities, performing the process in flow may remove such constraints, allowing more extreme conditions such as elevated temperatures and pressures to be explored with a view to accelerating the process kinetics, while reducing the risk of stability issues. With most batch processes, critical process parameters are developed and tested throughout the development and validation stages, but quality decisions and material disposals are often based on offline batch representative testing. In contrast, continuous flow allows for real-time feedback so that potential disruptions can be realized, captured and solved with an appropriate control strategy, avoiding a scenario where an entire batch is put at risk.

Improved safety is another big driver for continuous flow technology for reactions that are difficult or dangerous to do in batch reactors. As the reactions are carried out on a much smaller scale, energetic chemistries and toxic compounds can be handled with far less risk.

Improved safety is another big driver for continuous flow technology for reactions that are difficult or dangerous to do in batch reactors. As the reactions are carried out on a much smaller scale, energetic chemistries and toxic compounds can be handled with far less risk. Unstable intermediates and final products can also be handled more efficiently, as the rapid timescale of continuous flow reactors minimizes residence times, reducing and potentially eliminating the impact on safety and quality. Using continuous flow to handle high-energy products and reagents safely also removes the need for batch operations to be carried out in bunkerized production facilities that are expensive to set up and maintain.

Accelerated development

Adopting continuous flow in early-stage drug development can shorten the development phases and reduce the overall time to market. Introducing the process in early clinical development offers opportunities for optimization by choosing the ‘best route’ rather than the one best suited to a facility’s capabilities. As well as a compound typically being obtained in a quicker, cleaner manner, using continuous flow makes it possible to start building a process that can be commercially viable from the outset, reducing the potential multiple iterations of a development cycle as the compound progresses from phase to phase. Continuous flow is scalable from the outset, allowing manufacture to increase quickly from a few hundred grams of a compound to larger quantities by increasing the scale of the equipment, increasing the number of reactor vessels, or by extending the processing time.

Continuous flow allows multiple reactor modules to be linked together, enabling the same equipment and processes to be used at commercial scale as for development or pilot scale. This overcomes the scale-up challenges posed by the variations in equipment design that are often found between facilities or through different phases of process development.

Future development

With continuous processes becoming more widely adopted by the pharmaceutical industry, development work on finding efficient routes for manufacturing greater numbers of APIs is increasing, especially as regulatory agencies are also becoming more supportive of flow chemistry. As companies continue to develop new drugs, especially for niche, targeted indications where only small quantities of API will be required, flow chemistry will increase in importance and become part of the wider toolkit for development and production of medicines in coming years.

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A telescoped continuous process installed into a customer’s walk-through hood.
Flow Chemistry

In full flow – continuously battling bacteria with boron

How can the increasingly large problem of bacterial multi-drug resistance be tackled? Selective inhibitors of bacterial serine proteases used clinically in combination with β-lactam antibiotics may provide the answer.

Increasing multi-drug resistance to antimicrobial agents, particularly in Gram-negative bacteria, is a significant global health care challenge, for example, carbapenem-resistant Enterobacteriaceae (CRE) has been declared as one of the most urgent drug-resistant threats in the US. Much like the cephalosporin class antibiotic as one of the most urgent drug-resistant challenge, for example, carbapenem-resistant bacteria, is a significant global health care threat. Increasing multi-drug resistance to antimicrobial agents is a major concern, and selective inhibitors of bacterial serine proteases have been clinically used in combination with β-lactam antibiotics to redress the balance.

One recently approved inhibitor that targets KPC, Vaborbactam (Figure 1), is unusual in that it relies on a central boron atom to immobilize the bacterium's defensive enzymes, enabling a co-administered antibiotic, Meropenem, to block its activity. Subsequent rearrangement to generate the required chain-extended building block. The homologation is carried out in the presence of zinc chloride, which both promotes high levels of diastereoselectivity (due to chelation control in the transition state) and suppresses epimerization of the chlorinated product. The requirement for low temperature generation and processing of the organometallic species stems from its instability at higher temperatures, resulting in decomposition via formation of a carbene through α-elimination of LICI.[6] This organometallic-boronate methodology has been further developed by Agerawal and applied to a number of other complex synthetic targets.[7] Scale-up of low-temperature organometallic chemistry in batch is intrinsically challenging for a number of reasons. The ability to remove the heat from the reactor during exothermic additions at cryogenic temperatures is difficult and often very high dilutions and slow addition rates are required to maintain control. This in turn can decrease efficiency and productivity. Poor mixing, particularly at the point of addition, can also generate localized hot-spots and variable local stoichiometries resulting in formation of impurities and impacting yield and product quality. Continuous processing is frequently used to mitigate problems of this type encountered during batch processing. Flow chemistry is often the preferred approach in scaling up chemistry that utilizes highly reactive organometallic reagents such as organolithium or organomagnesium derivatives, including unstable species such as the lithium carbamids utilized in the Matteson reaction.[8,9] Situ formation and extremely rapid trapping of the organometallic species before decomposition can occur is possible under flow conditions but is poorly achieved in a large batch reactor.

The Matteson homologation, used to assemble the pivotal Vaborbactam-α-chloroboronic ester intermediate (Figure 1), is eminently amenable to a flow chemistry strategy. Based on early pioneering work by a team at Novartis in which millisecond generation and trapping of dichloromethylithium at higher temperatures under flow conditions was demonstrated,[9] Christian Schuster’s team at Patheon (Thermo Fisher Scientific), in collaboration with a wider group of industry experts, successfully utilized this technology, converting a lab-based model reaction into a continuous manufacturing process run on several-hundred-kilogram scale under full cGMP conditions in yields of 99%.10 The corresponding batch process proved unsuitable under laboratory conditions. Ultimately several tonnes of Matteson product were prepared in a process validation flow campaign enabling FDA fast-track approval and facilitating rapid development of Vaborbactam. To key the success of this work was a detailed investigation into the zinc chloride addition and developing conditions to prevent precipitated solids clogging the system—a hallmark of most flow chemistry processes. In early development work, the process flowstream was quenched into a bath vessel containing the pre-cooled zinc Lewis acid. This quickly became a bottleneck for increasing throughput, however. Two engineering solutions to this problem were explored, a continuous loop quench (mimicking the batch process) and a continuous stirred tank (CSTR)-based cascade quench. In the loop quench, boronate aduct was fed into a circulating pre-cooled solution of zinc chloride with reaction temperature controlled by heat exchangers. The product solution was pumped out and consumed zinc salt was continuously replenished in the loop reactor to keep the molar ratio constant. In the CSTR approach, zinc chloride solution was constantly fed to the pre-cooled vessel, the product solution exiting the CSTR in a cascade system controlled by an overflow device. The loop reactor system was ultimately selected to move forward and enabled the reaction to be run at a higher temperature and with better diastereomeric control. By leveraging the advantages a continuous process can impart, including increased process control, energy efficiency and reduced processing times, Schuster’s team succeeded in taking a difficult, unsolvable organometallic reaction to full-scale production. Another victory in the ongoing battle against the bacterial threat.

References:
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Figure 1: Matteson homologation approach to Vaborbactam.
All-natural calcium carbonate particles for formulating personal care products

This article explains how advanced, all-natural calcium carbonate particles offer multiple benefits for physical and sensorial properties of powdered personal care products and increase their appeal for the user.

When it comes to personal care products such as baby and body powder, consumers have a certain expectation with regards to their physical and sensorial properties. These include softness and pleasant skin feel, along with good absorption and a high stability and release of fragrance. Other key requirements include effective lubrication and coverage, along with heat stability.

High-purity calcium carbonate ticks all of those boxes – and more. This is the reason why Swiss-based global specialty ingredients supplier Omya, with expertise in calcium carbonate spanning more than 130 years, has used its in-depth knowledge to develop a safe, mineral-based solution specifically for powder applications.

Multiple benefits

Key to this innovation is a calcium carbonate functionalized by hydroxyapatite – a combination that delivers a smooth, soft-to-the-touch body product that has been proven safe for even the most sensitive of skins. The key to this innovation is a calcium carbonate functionalized by hydroxyapatite – a combination that delivers a smooth, soft-to-the-touch body product that has been proven safe for even the most sensitive of skins.

Proven qualities

To confirm the performance of its FCC solution, Omya conducted several comparative studies to analyze and compare the powder’s sensory properties against standard market references. The first trial was conducted on 20 healthy adult subjects with sensitive skin. Skin irritation was measured by a qualified dermatologist who scored the participants on a scale of 0 to 10, with 0 indicating no occurrence of edema and erythema, and 10 demonstrating full-scale irritation. Trial results clearly proved that the functional particles did not induce any irritation on sensitive skin, with the conclusion that they are safe for use on all skin types without fear of irritation.

Additionally, the products underwent a sensorial descriptive analysis following ISO 13299 by a panel of eight assessors. The sessions were performed in a room dedicated to sensory analysis and compliant with UNI ISO 8589 standard. Sensorial attributes such as colour, cushion effect, spreadability and smoothness were observed by trained panelists. In summary, the data showed that the new mineral innovation has a sensorial profile equal to those of standard market references.

Superior moisture absorption and fragrance release

Also tested was the water absorption capacity of the calcium carbonate ingredient, as well as its ability to release fragrance. Both the market reference and the Omya solution were exposed to various grades of relative humidity (RH) with subsequent measurement of the increase or decrease in mass. An increase in weight obviously demonstrates the capacity of materials to hold moisture.

The results revealed that the company’s new ingredient concept almost doubled the capacity to absorb moisture. Compared to conventional powder solutions, improved efficiency is demonstrated in absorbing and holding body fluids like urine, sweat and sebum, therefore keeping body areas dry and acting more effectively.

With regards to the release of fragrance, scent was loaded onto the powders – both the reference sample and the Omya solution – which were kept at room temperature in airtight jars. The release of fragrance was checked at a temperature similar to that of the skin (37°C) on the same day, and again after 30 days of storage. The results revealed that the loaded particles had a superior fragrance release capacity compared to market references. Furthermore, even after 30 days, the solution had no degradation of fragrance compared to the market reference.

Breakthrough in body powder

In conclusion, the Omya innovation was considered comparable to the reference sample in terms of colour, spreadability, whitening effect and smoothness, but with enhanced water absorption and fragrance release – both vital attributes in body powder products. Clearly, these result mean there are major opportunities for new product development with all-natural Omya particles as a natural alternative in the baby care and body powder segment, and beyond. “Our sustainably sourced ingredient solution is a breakthrough in body powder innovation,” says Tanja Budde, Head of Innovation and Technical Marketing, Consumer Goods at Omya International AG. “We know how important natural products are to consumers, particularly when it comes to skin care and other cosmetics. Our calcium carbonate-derived body powder ingredient will therefore be a key driver in this category. That’s because it is an entirely natural, ultra-pure, mineral-based ingredient which has been proven safe for use on even the most sensitive of skins.”

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Sensitive skin is an irregular condition that causes several issues regarding the skin aspect including rash, itch, redness, dryness, and discomfort. It is caused by the reactivity of the skin to environmental conditions and/or external and inner factors, including immunological and individual susceptibility. The prevalence of reported sensitive skin worldwide is very high - 14% for normal population. Regarding skin’s self-defense, one of several mechanisms is related to the endocannabinoid system, formed by a net of lipidic signals that can modulate both neural and inflammatory functions through a bidirectional interaction with different receptors:

- CB1 – One of the most common receptors in the entire nervous system - moderators of your memory, mood, motor function, perception of pain and responsible for the psychoactive properties of cannabis when THC binds to them
- CB2 – Most often found on the cells of our immune system - mediates immunomodulatory and inflammatory properties

The CB1 and CB2 receptors are distributed throughout the body, but particularly for CB2, it is found in higher density on the peripheral tissues (epidermis and dermis). The CB2 receptor is activated by endogenous (endocannabinoids) or exogenous ligands (generally agonists). As an example of exogenous ligands, we can point out the phytocannabinoids.

The most known phytocannabinoid is the cannabidiol (CBD), an active derived from hemp that has an affinity for both receptors and is known by its anti-inflammatory activity, however its use is still controversial due to the fact that may contain tetrahydrocannabinol (THC), related to psychotropic effect and with almost no studies regarding its possible side effects.

As an alternative to cannabidiol (CBD), another natural phytocannabinoid is the β-caryophyllene, present in the BERACARE CBA, a blend of amazon oils, from Beraca, which can modulate cell signs and consequently, attenuate inflammatory effects (decreasing levels of cytokines such as IL-1β and IL-6) with no activity in the CB1 receptor.

The β-caryophyllene is a CB2 receptor agonist. When it interacts with the CB2 receptor, it naturally acts through the interaction with the surface molecules and the inhibition of the Toll-type receptors, which is a type-1 protein family.
part of the innate immune process3. It is important to note that the action on TRH-type receptors leads to pro-inflammatory cytokines expression, thus these cytokines are not delivered and, consequently, persistent anti-inflammatory activity is formed.

Besides the activity of β-carapophyene for CB2, it also occurs a secondary activation related to β-endorphin, that is a neurotransmitter (also presented in the skin) related to immunological functions… that are produced as a cutaneous immune response. The β-endorphins are peptides formed by 31 amino-acids and produced in the brain, present in skin cells and delivered by opioid receptors. These compounds are resistant to enzymatic degradation and act directly on the immune system. One of the main effects of β-endorphins in the body is its analgesic effect.

Particularly for skin cells, β-endorphins production is directly related to comfort, calm, and relaxing, helping in the tissue’s reepithelization and recovery (skin healing). To study the β-carapophyene – CB2 activity, efficacy tests were performed in pridactical assays (ex vivo) tests anti-inflammatory activity, based on human skin culture that underwent inflammatory stress actions (on interleukins IL-1β and IL-6) andforts β-endorphin production. The Amazon oil complex (β-carapophyene rich) showed a reduction in inflammatory interleukins secretion and mediation of the immune system by the CB2 receptor activation, with a direct impact on tissue repair and maintenance of the skin balance. The balance – or skin homeostasis – allows the improvement of the natural cutaneous tissue ability of the recovery process.

The complex was able to act on the skin inflammatory response control, with a significant 55.4% and 25.2% reduction in the inflammatory interleukins IL-1β and IL-6 respectively, besides a 92.3% significant increase of β-endorphins production. Thus, these results indicate an anti-inflammatory activity that may favor both skin healing and reepithelization, according to the Graphs 1 and 2 respectively.

Finally, efficacy tests have proven important benefits of the Beracare CBA for beauty. The ingredient will help to mitigate the effects of premature aging related to inflammatory stress and it can support the re-epithelization and healing process due to the increased β-endorphin production. Beracare CBA is an ingredient with wellness and de-stressing properties, promoting various skin benefits such as calming, improved healing activity and providing comfort. In addition, the product is a safe alternative to CBD, with the versatility of applications in different cosmetic products.

**Bibliography:**


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**Figure 2.** The effects of BERACARE CBA on β-endorphin production in human skin culture in the presence of absence of lipoteichoic acid (LTA) at 100μM.

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Cosmetics

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Consumer-led demand for ‘clean-beauty’ products and an increased focus on sustainability has led to a continued drive for ingredient transparency within the cosmetics and personal care industry. The term ‘clean beauty’, coined by key cosmetic brands and consumers with a sustainable focus, is broad and largely undefined but refers to natural, environmentally friendly and sustainable products.

“A new generation of consumers wants a clean conscience when it comes to purchases, with 42 per cent of UK personal care consumers now buying natural and organic personal care products because they believe they are better for the environment,” says Thomas Kerfoot, co-founder of O&3. (Photo: O&3)

We champion openness in the industry with our technical database on our website, which offers transparency around our ingredients and support for our customers online. We want to arm R&D teams with everything they need to make decisions, including our products’ origins and manufacturing processes

Natural oils from O&3 help meet consumer demand for more natural-ingredient based cosmetic ingredients. (Photo: O&3)

Natural-product-based ingredients: reassurance and transparency

“Natural-product based ingredients provide reassurance and ingredient transparency, while also facing into the big issues of sustainability and quality,” Kerfoot adds. “However, using entirely natural ingredients is not necessarily the easiest option when approaching formulation. This is because natural ingredients are subject to a certain volatility. A change in harvest, weather patterns or even farming techniques could drastically change the make-up of the ingredients. Consistency is hard when it comes to the profile of a natural ingredient – which is why it’s key to work with natural oils experts, to manage any challenges. Although synthetic ingredients can be seen to be more consistent, there are major drawbacks: in our opinion, they are not always as functional as a natural ingredient. We believe the marketability factor of synthetics to be low in a world where consumers want products to be fresh and clearly produced in a natural environment.”

Growing the business

“As a family start-up, we take a lot of responsibility for supporting and enabling other start-ups,” says Kerfoot. “We have an ethos of not turning our noses up at small quantities, and we can match start-ups for speed and agility in ways some of the more established manufacturers can’t. There’s something special about working with other young, dynamic businesses to help them succeed and ultimately grow together. “We truly believe this is only the beginning and as a family team we are all committed to the long-term journey. O&3 is well set for sustainable growth in the future, through long-term partnerships with clients around the world,” he concludes.

References

An introduction to the world of nanocoatings

By Liam Critchley, Freelance Chemistry and Nanotechnology Writer

Despite being one of the longest standing industries, the coatings sector continues to advance and innovate. Recent advances in nanotechnology and coating methods have led to the creation of a new, more advanced class of coatings known as nanocoatings.

Coatings are used on materials in almost every industry, and the average person will be familiar with why coatings are used. For many coatings, you can physically see the coating being applied with the naked eye, and you can often tell if a material has been coated in some way. Coatings have been a keyway over the years for protecting materials, dissipating heat, and for helping to improve the conductive effects of a material and/or component. But what about a coating that you can’t physically see on a material, or being applied to a material? There are a number of next-generation coatings out there which require a nanoscale layer above the material and their effects are becoming increasingly important. These coatings that you cannot see are nanocoatings and can be used to improve the properties of a product without altering its aesthetics.

What are nanocoatings?

Nanocoatings, as the name suggests, are a nano-sized coating—where the molecules are all connected to each other and the underlying material through direct (covalent) bondsto form a very strong nanostructured network. The key feature about a nano-coating where the molecules are composed of approximately 10 nm thickness. The composition of nanocoatings can vary, with some containing just one element, some containing the same composition throughout but with a number of elements, while others have specifically designed layers where each layer plays a different role in achieving the desired functionality. The defining feature that governs whether a nano-coating is a nanocoating is the thickness, as the chemical composition can be anything so long as it is not greater than 100 nm.

Nanocoatings typically follow the same vein as traditional coatings, in that they are typically used for protecting a material, increasing its surface functionality (for example, to make it hydrophobic or oleophobic), the chemical composition can be anything so long as it is not greater than 100 nm. Nanocoatings have their own benefits—such as new functionality out of a coating application. But there are some common examples of why people use nanocoatings. For example, nanocoatings are becoming a very popular option (both commercially and in academia) as coatings for electrodes—for both batteries and other small devices. In these instances, enhanced electrical conductivity, oxidative resistance and heat dissipation properties can be induced to make the electrodes perform more optimally and for a longer time. Another example is coating windows or glass substrates to make them UV and heat resistant, while other examples include making surfaces more catalytically active, antibacterial in nature, insulating/dielectric, or hydrophilic/diaphotic. In a different vein, nanocoatings can also be used to change the optical properties of an active material within a device (e.g. photodetectors). Nanoparticles can even be coated despite their small size and spherical geometry to improve their functional surface properties. These are just a few examples, but they encapsulate the range of possibilities possible with nanocoatings, and there are many more.

Regardless of the specific intended effects, all nanocoatings that are deposited in a professional manner by industry will be highly uniform, conformal to the material, will completely cover the desired area, and will often be free of pinholes i.e. holes in a coating that can let in moisture or other undesirable molecules. Such uniformity and coverage at the nanometric level is something that you don’t often see with other coating methods and is one of the key formed by all nanocoatings possess, regardless of the specific application benefits they induce.

How nanocoatings are produced

There are three main ways of producing a high-functional nanocoating, using the so-called bottom-up deposition techniques—that is, techniques which build the coating up at the atomic level from scratch by depositing atoms on top of each other and enabling them to fuse together. These are chemical vapour deposition (CVD), physical vapour deposition (PVD) and atomic layer deposition (ALD).

Now, there are many wet chemical methods—such as sol-gel methods, spin and dip coating of nano-formulations, and ion-beam evaporation, and laser ablation. In the different PVD methods, a solid material is vapourised, moves as a gas through a reaction chamber and condenses on the material’s surface, forming a nanocoating. Atomic layer deposition (ALD) is often seen as a CVD variation but, there are enough operational differences for it to be considered its own class of nanocoating techniques—of which, again, there are few specific methods which enable a number of materials to be coated. ALD methods are also some of the more complex methods, but they often provide the best uniformity and coverage of all nanocoating deposition methods. ALD is a sequential deposition method that enables different molecules to be deposited in the same run, but both molecules are never present at the same. So, one precursor gets deposited on the surface, followed by the other, in a contiguous pattern until the desired thickness is obtained. This is known as a layer-by-layer (LbL) deposition method. As the molecules are deposited, the reactions between the molecules and the surface form the first layer of the coating bonding them together chemically and the subsequent layers deposited on top also chemically bond to the previous layer. The result is a layered nanocoating where all the layers are covalently bonded to each other, regardless of the geometry of the surface.

In conclusion

Nanocoatings are not for everyone. In applications where the active properties of traditional coatings provide more than enough benefit, then the extra cost associated with nanocoatings is not feasible. If more functionality or slightly enhanced properties are required in these scenarios, then adding in nanomaterials into the coating formulation and applying through conventional methods can be enough to provide the desired enhancements. However, when the application requires, and the cost is not a barrier, then nanocoatings offer a bespoke and tailored way of getting the maximum degree of functionality out of a coating because the chemical composition can be tailored to suit almost every need—regardless of whether a single layer or multiple nanoscale coating layers are required to achieve the desired effect.

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Quality system management for CDMOs

How to deal with multiple regulatory and customer requirements

The evolution of the CDMO market

Fine chemistry CDMOs have been historically involved in supporting the pharmaceutical sector but, over the years, they changed their business practices by following the identified needs of customers and the market, as well as by modifying their own services and technologies offerings. Thus, CDMO portfolios were often widely extended to serve players in such various industrial markets as food flavours, food supplements, fragrances, photographic chemicals, and agrochemistry, among others. Each customer and/or product, subject or not to regulations, has its own specific quality standards that need to be applied, and as a CDMO La Mesta Chimie Fine has to comply with these too.

Growing numbers of requirements in various industries

Over the past 10 years, in addition to the pharmaceutical industry’s large number of regulatory requirements, the CDMO sector has had to take into account the increasing regulatory standards of the big players in cosmetics, flavours & fragrances, photographic chemicals, and so on. The aim of all companies in these sectors is to always guarantee the best quality and traceability of products for their own customers, as these products are actually used by the wider public.

Requests for complying with various standards have therefore to be fulfilled. In addition to ISO9001 and GMP Part II compliance, La Mesta decided to apply for FSSC22000 certification (Food Safety System Certification), which it recently obtained.

The genesis of a global quality system

This latest move meant that the company had to address the following issues:

How to implement and maintain a Quality System meeting all the requirements without completely disrupting the one already in place
How to develop, apply and maintain a Quality System in an appropriate and proportionate manner for the highest-regulated products without making any non-quality, for the lowest-regulated products without making any ‘over-quality’, and without affecting the size and diversity of the company’s activities and standards. This might appear to be a tedious task and be difficult to perform in an industrial context but what if the benefits that could be accrued from an understanding of these standards and from experience of the company’s own practices could lead to a more pragmatic approach and the development of a ‘global’ Quality System?

La Mesta therefore decided to take a three-pronged approach: a global Quality System approach; risk assessment; and pragmatic adjustment of procedures and practices to achieve a practical Quality System satisfying the company’s needs.

Quality System approach

First, the requirements of ISO9001, FSSC22000 (including ISO22000) and
Information enabling risk assessment
Risk management is an important part of La Mesta’s activity in the areas of SHE, quality, business and so on, but the continuous search for zero risk can be very expensive and the need for the company to be profitable forced it to devote its efforts to essential goals. Thus, in the area of quality in its pharmaceutical and food industry activities, risk-taking was limited by the precautionary principle of patient or consumer safety. ICHQ9 principles and HACCP methodology applied, respectively, in these two highly regulated industries helped La Mesta to identify action paths that would enable it to put in place its global system. Company management therefore internally shared knowledge of regulatory requirements, processes, technology, and products to develop robust and efficient ways of managing quality risks.

Pragmatic approach to quality
Instructions and practices
The quality of a product is guaranteed by the manufacturing practices that are in place. La Mesta therefore adapted its practices based on risk assessment, keeping in mind regulatory and customer requirements, as well as the final end use of the product, with a focus on modifying instructions and control levels to meet these requirements.

The tools
Knowledge of processes and regulatory and customer requirements is essential in order to adapt practices and to specify clear instructions. Staff training and communication are also crucial. La Mesta therefore differentiated its documentation using different colours and logos to identify what type of product they referred to and the company also set up a simpler product release process that could be used where applicable.

This pragmatic approach led to the achievement of exactly just the right level of quality for each product and the correct application of the company’s strengths, resources, and time, producing a Quality System designed to meet regulatory and customer requirements and in which staff, and particularly operational staff, could see how they contribute to this. A quality culture has therefore become and is becoming even more important in the company.

In conclusion
To summarize: a fine chemistry CDMO may be seen as a toolbox with the ability to perform various projects thanks to its operational and technical agility, its compliance with increasing standards being simply an additional tool that meets the expectations of customers and satisfies regulations.

However, even in the area of Quality, CDMOs have to show agility in applying the relevant resources to meet the regulatory requirements of an individual project. Knowledge, pragmatism, risk assessment and a quality culture are the keys to success in this field and a Quality System should become a major asset that enables CDMOs to win business, perform successfully and remain attractive to customers in the markets it supplies.

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Rethinking pharma packaging to better model shelf life

Kori Anderson, General Manager, Healthcare Packaging at Honeywell, explains how a new collaboration between Honeywell and FreeThink Technologies combines the companies’ respective expertise in packaging technologies and stability studies to provide a new generation of packaging that results in longer shelf lives for medicinal products.

Last year Honeywell established a collaboration with FreeThink Technologies, a specialist in the science and technology of stability studies, to add FreeThink's predictive shelf life modeling to its existing suite of Healthcare Packaging services, combining Honeywell's expertise in managing formable, moisture barrier film with FreeThink Technologies' know-how of chemical and physical stability and accelerated shelf-life modeling for a wide range of products, including medicines. The pharmaceutical and related industries can benefit from the alliance through selecting the optimal blister packaging, including, where appropriate, the suitable grade of Aclar film for solid oral drugs based upon accelerated degradation data, comprehensive kinetic modeling and robust statistical analysis carried out by FreeThink Technologies. Honeywell and FreeThink’s combined service offering now supports pharmaceutical customers, including originator, generics, OTC and adjacent industries in all phases of development with an accurate model for a product’s shelf-life and stability in as little as four weeks.

Improved packaging: Aclar films

Honeywell’s Healthcare Packaging business includes the production of Aclar and Aclar Accel barrier films, which help pharmaceutical packaging companies lower total packaging costs, improve the flexibility of operations, and increase overall profitability. Aclar films are based on poly(chlorotrifluoroethylene) (PCTFE) fluoropolymer technology. They are crystal clear, biochemically inert, chemical-resistant, nonflammable, and plasticizer- and stabilizer-free. The films can facilitate increased patient compliance with doctor prescriptions with see-through, portable and patient-friendly pack presentations. Aclar formable films are used in a broad range of markets including originator and generic pharmaceuticals, and OTC pharmaceutical and animal health packaging.

Aclar barrier films, which help pharmaceutical packaging companies lower total packaging costs, improve the flexibility of operations, and increase overall profitability. Aclar films are based on poly(chlorotrifluoroethylene) (PCTFE) fluoropolymer technology. They are crystal clear, biochemically inert, chemical-resistant, nonflammable, and plasticizer- and stabilizer-free. The films can facilitate increased patient compliance with doctor prescriptions with see-through, portable and patient-friendly pack presentations. Aclar formable films are used in a broad range of markets including originator and generic pharmaceuticals, and OTC pharmaceutical and animal health packaging.

Rethinking pharma packaging to better model shelf life

Kori Anderson, General Manager, Healthcare Packaging at Honeywell

Modelling shelf life and stability

Honeywell says its partnership with FreeThink will enable its customers to select the optimal blister packaging, including where appropriate, the suitable grade of Aclar film for solid oral drugs based upon accelerated degradation data, comprehensive kinetic modelling and robust statistical analysis carried out by FreeThink Technologies. The combined service will support pharmaceutical customers, including originator, generics, OTC and adjacent industries, in all phases of development with an accurate model for a product’s shelf-life and stability in time periods as short as four weeks. The company says the collaboration will provide its customers with reduced packaging cost, shorter time to market and greater confidence when making primary packaging decisions.

FreeThink’s predictive modeling service was founded on the peer-reviewed and widely adopted Accelerated Stability Assessment Program (ASAP) which provides credible product expiration dating based on confidence levels derived from experimental design and statistical data analysis, while the company’s laboratories apply their extensive expertise in rapid product shelf-life determination with the proprietary software, ASAPprime, which provides statistical modelling from experimental data.

Avoiding overpackaging

A typical example of how Honeywell’s and FreeThink’s combined service can assist pharmaceutical companies that are very mindful about packaging costs is in avoiding overpackaging by providing a prediction of the barrier level (Aclar grade) needed to achieve the target shelf-life of a generic product under development. Another example of the applicability of this new offering is the assessment of the impact of protective barrier packaging on product shelf-life for planned launches, including site transfers of the same product in different climatic zones. This often requires an upgrade in protective barrier, and the extent can be effectively predicted using the experimental data gathered during a four-week ASAP study. According to Honeywell, this service enhancement is aligned with its end customers’ evolving need for optimized packaging solutions and is in line with its efforts and commitment to improving the user experience with its products.

Market expansion: conforming to different regulations

With the increased focus on innovation in packaging in the pharmaceutical industry, pharmaceutical companies have made rapid strides in developing new molecules and new production techniques to conform with global regulatory standards as well as local and multinational pharmaceutical companies continue to expand into highly regulated markets such as the US and Europe, organizations seek to provide the highest-quality products in a rapidly evolving regulatory landscape. Given the expected growth of the pharmaceutical packaging market by 2023, companies will require new packaging technologies that allow them to launch drugs faster while reducing operational costs. Honeywell’s technology is designed to provide a better shelf life for medicines and support companies in meeting new regulatory requirements.

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Effectively crafting your process development

What is needed to drive effective process development? Understanding how to take a holistic approach to the technical, economic and regulatory factors underpinning your chemistry is crucial. Dr Alan Steven, Senior Principal Scientist at CatSci, explores...

Behind every approved therapeutic should lie an environmentally and economically sustainable manufacturing process, enabling the drug substance asset to be made as efficiently as possible. As part of this drive to meet the evolving healthcare needs of the world, three broad areas of the drug substance process development must be undertaken.

These are as follows: establishing a sequence of intermediates used to make the active pharmaceutical ingredient (API) or its precursors, developing reagents and solvents used to convert one intermediate into another, and studying a transformation to build a fundamental understanding that allows processes to behave reliably and robustly in a manufacturing facility.

When a contract research organization (CRO) commences a process development project, the customer could want the knowledge for, and access to, a set of manufacturing processes that achieve some or all of the above. This requires the comprehensive consideration and evaluation of various routes under a plethora of processing conditions – a complex operation akin to playing a game of multidimensional chess.

A holistic approach for success

In order to reach a checkmate with your manufacturing process, there needs to be careful consideration of process chemistry, crystallization science and analytical science. All are important and should not be developed independently of each other. With respect to analytical method development, it is critical to avoid defaulting to a particular technique and instead choose an approach best suited for yielding information on the quality attributes of the chosen product. Consider your analytical method as a process as you would the chemistry, with numerous inputs, which could include variables such as flow rates, sample concentration and eluent pH.

When developing the chemistry, one of the most technically challenging areas is catalytic reactions. While this can provide significant rewards, understanding the catalytic cycle requires significant investment in tools and expertise. Moreover, the reaction performance can be negatively affected when the quality of an input material is slightly changed. Another important consideration is that while a catalyzed reaction may present a favourable environmental profile, the whole set of approaches must be considered holistically. This means that you should weigh up the reaction yield and selectivity against others perceived as being outside of the reaction process, such as the sustainability of using the catalyst metal and ligand under consideration.

Crystallization scale-up is arguably an under-appreciated area of process development science. There is no point in developing an efficient way of making crystalline bonds in your synthetic route if you have challenges isolating the material. As well as having the scope to purge impurities, it’s also important to comprehend how crystallization and isolation can impact manufacturability and processing times across different scales.

Making your process viable

It is clear that scaling up is a significant technical challenge that could impact the long-term viability of a processing option. Process development scientists may hit a roadblock when having used a set of processes or products in the earlier stages of the project and manufacturing at larger volumes does not proceed as expected. Any reduction in mass transfer efficiency when increasing the scale can affect the rate and impurity profile of a reaction. This can be overcome through careful process development and reducing the number of phases present in a reaction solution.

Aside from technical challenges, another significant influence is the economics impacting the feasibility of a process. For example, a particular reagent could drastically improve yield, but there may be no industry standard for manufacturing it in a cost-effective manner. Only when the drug has reached the market could this change through the increase in generated demand.

Differing regulatory considerations also have a substantial impact when evaluating the viability of a process. Take the different attitudes to nitrosamine impurities that may track through to a drug substance. Some authorities will require rigorous testing, whereas others are led by scientific evidence indicating no chance of the impurity reaching the final product. Being able to respond and accommodate these contrasting attitudes is critical.

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