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Pharma’s Decade in Brief

As the new year begins, it is always useful to take stock of the innovations that have occurred in the pharmaceutical industry during the previous 12 months. And, as this year heralds the start of a new decade, what better time than to take a look at some of the biggest, brightest, and boldest happenings from the industry over the past 10 years.

1. Brexit
Yes, inevitably Brexit needed to be on the list as it is a topic that has dominated headlines across Europe and is still impacting the pharmaceutical landscape. With the United Kingdom set to leave the European Union at the end of January 2020, Brexit will straddle two decades and has the possibility to significantly alter much within pharma, such as regulatory processes and supply chains, across the European region.

2. EMA relocates
Another big event to impact the European pharma industry over the past 10 years is the relocation of the European Medicines Agency (EMA). As a result of the UK’s referendum decision to leave the EU, relocation of EMA from London to Amsterdam, a country located within the EU, was an inescapable consequence. This upheaval has caused many disruptions, not least the dramatic reduction in staff of the agency itself.

3. Approval of cannabis-based medicine
The approval of Epidyolex (cannabidiol), which was granted in September 2019, represents the first within Asia led to regulatory action being taken, such as the requirement on pharma companies to check raw materials and supply chain processes. The ramifications of this quality issue are ongoing, and as is further explained in this month’s European Regulatory Watch, there is the potential that EMA will further tighten up rules around quality of imported APIs.

4. Anti-counterfeiting measures
The EU falsified medicines directive (FMD) was set out and implemented during the course of the decade, meaning companies across Europe are now required to include specific safety features on packaging of all medical products. These European regulations have been set out to ensure that medicines within the region are safe and properly controlled.

5. Nitrosamine impurities risk
Impurities found in sartan blood pressure medications that had been produced within Asia led to regulatory action being taken, such as the requirement on pharma companies to check raw materials and supply chain processes. The ramifications of this quality issue are ongoing, and as is further explained in this month’s European Regulatory Watch, there is the potential that EMA will further tighten up rules around quality of imported APIs.

6. BMS acquisition of Celgene
In 2019, the global pharma industry saw the acquisition of Celgene by Bristol-Myers Squibb (BMS), worth a whopping US$79.4 billion (€69.7 billion) (1). This acquisition represented the largest for the industry, in terms of financial value, over the past 10 years.

7. The opioid epidemic
This huge news item first hit headlines back in 1991, but it has, in a secondary and tertiary wave (2010 and 2013, respectively), been impactful for pharma and global human health throughout the past decade. Currently, there is a lot of news concerning the Sackler family in the United States, who are under scrutiny as a result of marketing tactics employed in the promotion of opioids, and in Europe, action is being taken by regulatory authorities and government bodies to try to avoid a crisis like that happening in the US.

8. Martin Shkreli
Although the arrest and subsequent imprisonment of Martin Shkreli (aka Pharma Bro) is a news story essentially from the US, it was closely followed by many in Europe. A former pharmaceutical executive and hedge fund manager, responsible for price gouging a life-saving drug 50-fold, Shkreli was actually arrested in 2015 and eventually imprisoned in 2018 for fraud.

9. First CAR-T cell therapies approved in Europe
In August 2018, the European Commission granted approval to two chimeric antigen receptor T cell (CAR-T) therapies, Novartis’ Kymriah (tisagenlecleucel) and Gilead’s Yescarta (axicabtagene ciloleucel). These innovative personalized therapies offer a paradigm shift in treatment for patients with specific aggressive malignancies, as per the approved indications, and seem to be paving the way for more cell and gene therapy approvals.

10. Rise of biosimilars
Towards the end of the decade, there has been an increasing number of biosimilars launched within Europe. These biological products that have no meaningful differences to the originator product are offering a cost-sustainable option to healthcare systems and patients across the region. Of particular note are biosimilars to Humira (adalimumab), Amgen’s Amgevita and Biogen’s Imraldi, which were launched in October 2018.

References

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European Regulators Strive to Make Up for Lost Ground

In 2020, European regulators are expected to start to be even more active in encouraging drugs innovations rather than hindering them through legal restrictions.

The new year looks likely to be one in which the European Union’s medicines regulatory system makes a determined effort to ensure that advances in science and technology result in more innovative medicines being made available to patients in Europe. However, it is also likely to be a year in which regulators will be under even greater pressure to deal more effectively with chronic problems of medicines shortages and quality deficiencies in imported APIs.

It is also projected that 2020 will see the European Medicines Agency (EMA), responsible for the approval of medicines for marketing in the whole of the EU and for the coordination of the drugs licensing network covering the union’s 27 member states, strive to return to a level of normality after two years of disruption. Efforts to regain normality come after the agency’s relocation of its headquarters in 2017 from London to Amsterdam in the Netherlands after the United Kingdom voted to leave the EU in the 2016 referendum.

EMA only formally took over its new headquarters in Amsterdam in January (2020) after initially being accommodated in interim offices in the Dutch city. With the relocation leading to lower staffing levels, the agency has had to considerably curb its activities. It is also trying to cope with a squeeze on its budget at a time of increasing costs.

New year’s objectives

A major objective in 2020 for EMA will be to return operations to a pre-Brexit level. But with staff numbers being substantially reduced and constraints on its budget that seems to be a difficult task. Instead the agency could end up becoming a slimmer operation focussed on its core priorities of monitoring and evaluating the quality, safety, and efficacy of drugs during their development and throughout their life cycles.

The whole EU regulatory network headed by EMA is answerable to the DG Sante, the health directorate of the European Commission (EC), the Brussels-based EU executive, within which the advisory pharmaceutical committee is exercising a growing influence.

The committee, comprising officials of the commission, EMA, and EU member states, recommended in November 2019 that priority be given to the completion of on-going projects (1). These included action plans on pharmaceuticals in the environment (PIE), improvements in the regulatory environment for advanced therapy medicinal products (ATMPs), antimicrobial resistance (AMR), support for drugs repurposing, and on improving quality of APIs. But the commission itself has just changed its top management with a new president, Germany’s Ursula von der Leyen, and a new agenda, which will generate changes of focus in the pharmaceuticals area.

In healthcare, the new commission has set a number of priorities, such as affordability of medicines and patients’ access to innovative drugs, combating medicines shortages, encouraging through legislation digitalization in health services, and ensuring the effective oversight of the global supply chain in medicines. In addition, the new commission has launched a European Green Deal to take measures to combat climate change, cut pollution, and help companies develop clean products and technologies (2).

Regulatory tasks

The regulatory agendas of Europe’s medicines agencies at the EU and national levels will be dictated to some extent this year by the commission’s priorities. Among the most important regulatory tasks this year for the EU’s network of medicines licensing agencies will be the finalizing of a strategy covering regulatory science.

A draft EMA strategy on regulatory science to 2025 (3) was the subject of a consultation with a range of stakeholders during 2019, including industry, researchers, healthcare professionals, and patients’ representatives. Regulatory science is seen as a vital platform to fulfilling the mission of the EU medicines licensing network in translating science and innovation into more effective medicines and ensuring that patients have access to them.

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it and must be prepared for the future challenges it will present to us,” said Guido Rasi, EMA executive director, at a stakeholders workshop in Amsterdam on the agency’s regulatory science draft strategy in November 2019 (4).

The workshop was held to help in the finalization of the strategy early this year, particularly in sorting out the different priorities put forward by the various clusters of stakeholders taking part in the consultation exercise. The industry representatives in the consultation wanted priority to be given, for example, to novel manufacturing technologies and greater exploitation of digitalization technologies.

The final version of the strategy will be used as a basis for a five-year strategy for the EU’s medicines regulation network (EMRN). This document is due to be drafted by June for publication in October after going through a stakeholder consultation.

EMA and the Heads of Medicines Agencies (HMA) representing the national authorities already have a joint task force on big data identifying how digitalized data sets can be used to develop new and improved medicines (5). This work should provide key components of regulations on digitalization in the medicines sector. But EU regulators face a daunting job in the regulation of areas like data quality and standards for data analytics.

One important consideration is the need for the regulators themselves to have access to skills and training so that they can effectively evaluate the quality of large data sets and the analytics performed on them.

With the EU wanting to be a global leader in using regulation to encourage medicines innovation, it also wishes, through the European Green Deal, to be a pace setter in imposing safeguards on PIE. As a result, PIE tops the list of the current priorities of the commission’s pharmaceutical committee.

Other major objectives, which will be determining regulatory agendas in 2020—and probably much of the rest of the new decade—will be the assurance of secure, efficient, and clean supply chains extending from starting materials, APIs to finished medicinal products.

Brexit: Still a threat to supply chains?
In 2019, a big threat to these supply chains within Europe was a no-deal Brexit. Under this scenario, the UK—a leading medicines exporter and importer—would be relegated to the status of a third country under EU legislation without the protection even of a free trade agreement (FTA). Both the EU and the UK had to prepare provisional emergency measures to prevent serious medicine shortages due to the sudden introduction of customs checks and quality controls.

However, after the Brexit-supporting ruling Tory party won a UK general election in December 2019 by a substantial majority soon after clinching a withdrawal agreement, the country looks certain to finally leave the EU at the end of January 2020 with trade in medicines and other products remaining relatively intact. Its departure will be accompanied by a transition period of at least a year during which an EU–UK FTA would at least start to be negotiated with the relationship between the two sides staying substantially the same as if the UK were still an EU member.

But the danger of a no-deal scenario will not have been lifted completely. Despite warnings by trade experts that a full FTA will need longer than a year to negotiate, the UK government has indicated that if a trade agreement is not reached by the end of December 2020 it will leave without one, even though there would be an option for extending the transition period to continue negotiations.

The UK could be aiming for a short framework trade agreement with the EU in which regulatory standards, such as those on pharmaceuticals, could be thrashed out over several years. During this time, there would still be a considerable risk of EU–UK trade disruptions and hence medicines scarcities.

Other major issues
Even without the effects of the Brexit dispute, availability of medicines will still remain a major issue in Europe. In recent years, supply chains have been suffering from chronic shortages, particularly stemming from quality issues with APIs, most of which are imported from China and India.

Quality problems worsened with the discovery of nitrosamine impurities, first in late 2018 in Asian-produced APIs for sartan blood pressure medicines and then last year for the diabetes treatment pioglitazone and the ulcer treatment ranitidine. EMA had to ask all relevant pharmaceutical companies to check raw materials and processes in their supply chain for risk of production of nitrosamine impurities, which are classified as probable carcinogens.

Results of an EMA investigation into the episode with ‘lessons to be learned’ are due to be revealed in mid-2020, opening the way to a further tightening up of EU rules generally on checking the quality of imported APIs. Also, this will coincide with a decision by the EMA on the future scope of its operation in the light of a 20% reduction in staffing after its relocation and budgetary restraints.

By the end of the year, not only the rules on imported APIs will likely have changed, but the future of the agency mainly responsible for imposing said rules will have changed as well.

References
According to market research (1), the pharmaceutical packaging market is expected to grow at a compound annual rate of 8.3% during the period 2019–2025. Drivers for this growth in the pharmaceutical packaging market include rising demand from emerging economies, increasing efforts to improve life-expectancy, and more disposable income, among others.

In a report released by Pharmapack—the dedicated pharma packaging and drug delivery event—several trends, such as regulatory mandates, targeting niche disease areas, and patient-centricity, were highlighted as being important for the future of pharmaceutical packaging (2). This article explores the significant trends that have shaped the pharmaceutical packaging market over the past decade and those that have the potential to shape the future of the sector in more depth.

Uptake of serialization
Implementation of new regulations across global markets to combat counterfeiting has been touted as a major trend impacting pharmaceutical packaging over the course of the past few years. “The pharmaceutical packaging industry has seen an increased uptake of track-and-trace systems to prevent counterfeit products reaching patients,” says Marcelo Cruz, head of marketing and business development, Tjoapack. “This is partly due to the implementation of new regulations globally.”

In Europe, companies were required to comply with the European Union Falsified Medicine Directive (EU FMD) from February 2019. “The EU FMD requires all products to feature unique identifiers and anti-tampering devices to allow items to be verifiable at the point of dispense,” confirms Cruz. Similarly, companies in the United States have been required to comply with the US Drug Supply Chain Security Act (DSCSA)—a regulation that was implemented in 2014—which necessitates the inclusion of lot number, expiry date, and standardized numerical identifier on each drug product pack.

“These track-and-trace processes are now an integral part of the pharmaceutical supply chain and can significantly improve patient safety,” adds Cruz. “Likewise, the data these processes generate mean they can also help to streamline operations and logistics, increase visibility of the supply chain, and allow partners to more accurately forecast orders.”

Although these regulations coming into force have impacted the industry significantly, opportunities have also presented themselves for specialist companies in the fields of serialization and aggregation. “Many contract packaging organizations (CPOs) already had specialist knowledge of track-and-trace systems and the process of implementation. As such, these CPOs were able to offer this expertise to sponsor firms looking to outsource packaging requirements due to concerns around compliance,” notes Cruz. “This has afforded these CPOs a competitive advantage and made them a reliable outsourcing partner for their customers.”

Improved quality and focusing on the patient
For Dietmar Siemssen, CEO of Gerresheimer, a key trend impacting the pharmaceutical packaging
industry has been the increasing demands for improved quality. "A key factor for the pharmaceutical industry, in terms of packaging, is to prevent any potential risk to patients’ health," says Siemssen. "Therefore, the demand for the perfect packaging that guarantees the integrity of the drug has risen too. Pharma companies are moving increasingly towards zero-defect production and primary packaging providers are doing the same."

Material selection can also play a part in terms of quality, according to Anil Kumar Busimi, senior global product manager for Schott iQ Platform, Schott. "Borosilicate glass has been the first choice for parenteral packaging for drug manufacturers since its development in 1911 due to its excellent barrier properties and regulatory ease," he reveals. "Nonetheless, there is also another material, which is gaining interest, namely polymers (such as cyclic olefin copolymer). The physical stability as well as the diverse design options make it an attractive alternative for some drugs."

Newer materials and packaging designs offer design flexibility so that demands of the drug products, filling processes, and route of administration can be easily met.

Additionally, newer materials and packaging designs offer design flexibility so that demands of the drug products, filling processes, and route of administration can be easily met. This aspect is gaining importance for pharmaceutical companies as the healthcare setting is shifting away from the hospital and more towards home where the patient can administer treatment themselves. "As more and more treatments for chronic diseases are becoming available, we are seeing a strong trend towards self-administration and consequently a spike in device development," states Busimi. "The overarching goal is to make self-administration of injectable drugs (including biologics) easy and safe, while also improving patient adherence."

Compliance with a medication regimen and patient convenience have been important considerations for pharmaceutical packaging companies, adds Siemssen. "In the future, there will be an evolution of intelligent and connected drug delivery devices and pharmaceutical primary packaging," he notes. "These changes may be seen by the industry in the forms of complete solutions, platforms, or modular systems."

Concurring with Siemssen, Busimi highlights the attention that has been given to wearable devices and injector technology by the industry, particularly when used to deliver high-volume and high-viscous drugs in the home setting. "Large volume, on-body injectors need novel primary packaging solutions, which can keep the drugs stable, offer required container closure integrity, fit seamlessly with the device, and are easy to integrate in fill-and-finish operations," he stresses.

Moving away from the blockbuster and the rise of biologics

An industry trend witnessed by Busimi over recent years has been the shift from blockbuster drugs to personalized medicine. "Targeted therapies and other novel drugs are continuing to dominate the drug development pipeline, and the pharmaceutical packaging industry has started to explore new ways to package and store products in response," remarks Cruz in agreement with Busimi’s observation.

"The introduction of more biologics, such as monoclonal antibodies, cell and gene therapies, antibody–drug conjugates, among others, has had a direct effect on Pharma packaging," continues Busimi. "Such drugs are typically produced in small batches, pushing manufacturers toward leaner manufacturing operations. Subsequently, the demand for ready-to-use primary packaging components and flexible filling technologies is growing."

Furthermore, the sensitive nature of biologics means that they often require precise packaging material or specialist, temperature-controlled packaging, notes Cruz. "Packaging organizations need to understand the intricacy of packaging these products to ensure they can continue to service their customers," he says. "It's also important for companies to ensure they are mitigating the risks associated with improper packaging or storage. This added layer of complexity has driven an increase in demand for the services of specialist CPOs with this expertise in place."

Looking beyond the current trends

"When looking beyond the current trends, which will affect the Pharma packaging industry for years to come, we can say that the industry is developing a strong purpose driven mindset," states Busimi. "As health and wellbeing are highly precious to people, this mindset will be reflected in many future trends."

By way of example, Busimi continues to explain that it is Pharma packaging companies’ purpose to contribute to both patients and the Pharma industry, which will lead to increasing collaborative efforts to foster innovation. "The use of resource-efficient innovation models such as externally sourcing or cooperatively developing products in partnerships becomes fundamentally important in rapidly changing markets," he says. "The paradigm of open innovation and integrating the development of
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primary packaging and delivery devices early in the development will increase.”

For Siemssen, patient-centricity will continue to receive heightened interest and consideration in the future. “As more and more people around the world gain access to healthcare systems and healthcare costs continue to rise, focus on the patient and controlling costs will be of great import,” he notes. “Therefore, within the increasingly modern digital world, drug compliance and convenience for the user are key for the future with pharmaceutical packaging and delivery systems playing a crucial role in that health ecosystem.”

Adding to the discussion on patient-centric trends, Busimi highlights that digitalization in pharma and general healthcare will be a contributing factor. “The use of wearable devices for data collection and diagnosis, use of smart containers, smart drug delivery devices, and use of big data for optimizing the primary packaging as well as fill-and-finish operations will significantly transform the drug development to tracking patient outcomes,” he says. “This is further seen as a key enabler to reduce costs in the healthcare systems.”

Postponement packaging is a trend that will gain prominence in the future, according to Cruz. By implementing a more flexible packaging process, firms will be able to react more quickly to market demands and can potentially avoid costs that could be associated with recalls or variations in supply requirements, he explains.

“Another trend that is likely to impact pharma packaging over the course of the coming decade is that of full aggregation, which is effectively the next step beyond serialization,” states Cruz. “Aggregation essentially eliminates the need for a wholesaler to open a case and scan individual units manually, creating significant process efficiencies and lowering resource requirements, as well as ultimately speeding up a product’s passage through the supply chain.”

References
Prioritizing Sustainable Packaging

Pharmaceutical companies work toward a circular economy.

Concerned about waste, plastic pollution of the oceans, and resource depletion, consumers want packaging materials that are minimal yet protective, renewable, recyclable, reusable, and/or contain recycled content, with clear instructions for package recycling. To earn an eco-friendly reputation, packaging must be designed with sustainability in mind, which requires paying attention to all components, including inks and adhesives, as well as disposal scenarios. Many pharmaceutical companies, retailers, and other members of the pharmaceutical supply chain have set sustainability goals and are ramping up efforts to reduce waste in support of a circular economy.

AstraZeneca, for example, has several sustainable packaging initiatives underway, including the launch of a blister laminate that reduces waste, a mail-back pilot programme to collect used inhalers, and efforts to prevent pharmaceuticals from contaminating the environment (1).

Bristol-Myers Squibb (BMS) is working to meet a 2020 deadline for its current set of sustainability goals. Waste management is one focus. As a result, the company is conducting a software-based lifecycle analysis to assess the environmental impact of packaging materials used for certain products (2). The company also has eliminated polyvinyl chloride (PVC) bottles and trays and has reduced the use of PVC in blister packaging with the goal of eventually eliminating it entirely (3).

Other efforts include simplifying a packaging insert in accordance with recommendations in the company’s Sustainable Packaging Design Guideline. This change saved 70 tons of paper per year and allowed more product per pallet, which reduced ocean container requirements by 30%. The result? Resource conservation, waste reduction, lower greenhouse gas emissions, and a savings of more than US$2 million (€1.8 million) annually (3).

For BMS’s Orencia (abatacept), a Household Generated Sharps Management Plan offers guidance, instructions, and/or recommendations for handling and proper disposal of sharps. Users of the self-injected product also may participate in a no-cost, mail-back programme (4).

Promoting the circular economy

To support the movement toward a circular economy, several groups have developed guidelines for more sustainable packaging. A Recycling Playbook developed by Walmart in collaboration with Pure Strategies, The Association of Plastic Recyclers, and the Sustainable Packaging Coalition, helps suppliers pursue recyclable packaging and recycled-content goals (6). It discusses what type of plastic packaging is more easily recyclable, identifies recycling challenges for certain packaging materials, and supplements the Walmart sustainable packaging playbook, which describes best practices such as optimizing packaging design and using consumer-friendly recycling labels (7).

Greener packaging options

With high interest in renewable content, recycled content, and source reduction, packaging suppliers are introducing more environmentally friendly products. A collaborative effort by jARDEN Plastic Solutions, SACMI Group, and Milliken has developed a lightweight high-density polyethylene (HDPE) pharmaceutical bottle. The design depends on a barrier additive from Milliken and proprietary compression blow forming equipment from SACMI, which are used by jARDEN Plastic Solutions to produce thin-wall bottles that are up to 28% lighter than standard designs. The strong, lightweight containers offer excellent barrier performance,
require less energy to manufacture, and generate less scrap (8).

To improve the recyclability of tube packaging, Hoffmann Neopac has published the Tube Design Guide for Recyclability. As shown in Figure 1, it recommends a thin-walled body and shoulder consisting of PE or polypropylene (PP) with less than 5% barrier content, lightweight caps of the same material as the tube body, natural or light colouring, and minimalist graphics with solvent-free, ultraviolet-cured inks and varnish. “Sustainability and recyclability can be particularly challenging in the pharma sector, where packaging solutions must protect and preserve the efficacy of important medicines and complex formulations,” said Martina Christiansen, head of Pharma sales and marketing at Hoffmann Neopac. “We see this guide—and the tubes that can be produced by adhering to it—as an important step in an ongoing process to make pharma packaging more eco-conscious.” The company also offers an EcoDesign portfolio that includes the Recycled Tube, featuring 75% recycled, food-grade compliant PE; Sugarcane Tube, made from renewable raw materials and offering the same characteristics and processability as fossil-based PE; and PICEA Tube, comprised of 95% renewable material in the tube body and shoulder—including 10% spruce wood recovered from sawmill waste (9).

Sana Packaging makes cannabis product packaging using recycled HDPE sourced by Oceanworks, which intercepts and recycles plastics that impact the ocean. “Our first run of reclaimed ocean plastic cannabis packaging removed four tons (8000 lb) of plastic waste from our oceans,” said Ron Basak-Smith, co-founder and CEO of Sana Packaging (10). Sana Packaging also produces 100% plant-based cannabis packaging from hemp. Recycled polyethylene terephthalate (PET) containers have been introduced by Bormioli Pharma. Made from 100% pharma-grade recycled content, the containers exhibit transparency and physical and mechanical properties equivalent to virgin PET (11).

AptarGroup is partnering with PureCycle Technologies to commercialize the latter’s ultra-pure recycled PP for dispensing applications. PureCycle’s patented recycling process, developed and licensed by Procter & Gamble, separates colour, odour, and any other contaminants from plastic waste feedstock to transform it into resin with properties equivalent to virgin PP. “This critical partnership further reinforces our commitment to supporting a circular economy where products and materials are reused or recycled and do not become waste,” stated Stephan Tanda, president and CEO of Aptar (12).

AptarGroup also provides lotion pumps for several products available via Loop and is a partner in the global circular shopping platform established by TerraCycle. With Loop, consumers purchase products in reusable packaging and they arrive in a returnable Loop tote. Once empty, the consumer replaces the container in the tote and schedules a pickup. Returned containers are cleaned, refilled, and readied to reship, creating a circular product experience (13).

Another Loop partner, RB, offers several over-the-counter products via Loop. The effort moves the company toward achieving its commitment to making 100% of product packaging recyclable or reusable by 2025. “Reusable packaging is the future of consumption,” commented Nitish Kapoor, executive vice-president of the Health Business Unit for RB North America (14).

Renewable BioBase packaging is being launched by Sanner with the introduction of a 25 mm-diameter tube for effervescent tablets with matching DASG-1 desiccant closure. Biopolymers derived from renewable resources, such as bio-ethanol, achieve bio-based content above 90% and significantly reduce carbon dioxide emissions. “Bio-based packaging solutions have the same key characteristics as common packaging solutions; they can be processed on existing filling lines and can be recycled,” says Peik-Christian Witte, director of R&D at Sanner. In addition, says Witte, “compared to common tubes made of fossil resources, this solution can increase shelf life of the tablets due to a higher water barrier performance, which is an additional value-add for our customers. These features support waste reduction for both the packaging solution and the packaged goods.”

Sustainable packaging also is available for temperature-controlled shipments. The foam-free ClimaCell insulated liner from TemperPack now carries a How2Recycle label with the designation “Widely Recyclable.” “Getting the How2Recycle certification will help ensure that anyone who receives a ClimaCell
Packaging

product will know that it can be disposed of alongside the cardboard box or paper bag it came in,” said James McGoff, co-founder and co-CEO of TemperPack (15).

Liner thickness and density can be adjusted without major retooling to meet the needs of controlled temperature or frozen product. “ClimaCell liner options work with gel packs, ice packs, or dry ice and consist of a number of plant-based materials,” says John Briney, director of marketing at TemperPack. The company uses a combination of materials, including starch, to increase the hydrophobicity of the insulation, and wraps the extruded insulation in coated paper.

“Overall feedback on ClimaCell has been great, especially in the specialty pharmacy industry,” concludes Briney. “Most of the patients that were receiving [polystyrene foam] coolers had no easy way of disposing them and either stockpiled them or threw them away in their trash. We’ve received comments from a number of customers of how relieved they were to be able to recycle this new packaging, knowing it can be turned back into paper for other products.”

References

Packing a Punch in Paris

PTE looks ahead to 2020’s edition of Pharmapack—the pharma industry’s dedicated packaging and drug delivery event.

Felicity Thomas

February 2020 heralds the latest edition of Pharmapack—Europe’s dedicated pharmaceutical packaging and drug delivery event—which is expected to once again play host to a plethora of pharmaceutical manufacturers and packaging suppliers in Paris, France.

Over the course of two days (5–6 February 2020), visitors to Hall 7.2 at the Paris Expo, Porte de Versailles, will be able to network with peers and learn about the latest innovations, trends, and regulations advancing and impacting the fields of packaging, drug delivery, medical devices, and machinery. Event organizers anticipate more than 400 exhibitors and approximately 5400 attendees onsite at the show (1).

A new feature of the 2020 event will be the Machinery Zone, which will offer attendees the chance to visit with companies specializing in pharmaceutical packaging manufacturing machinery, technology, and equipment in a dedicated area of the exhibition floor. This new feature will add to the already existing platforms of the event, such as the Pharmapack Awards, Innovation Gallery, and Learning Lab.

Educational themes

One of the main pillars of Pharmapack is education, and for 2020’s event, the conference agenda has been set to tackle some of the more prominent and emerging issues facing pharmaceutical packaging and drug delivery companies. Separated into four sessions, spanning the two days, the conference programme will examine ‘Connectivity and Patient-Centricity’, ‘Sustainability’, ‘Challenges in Drug Delivery for Biologics’, and ‘New Horizons in Innovation’. (For a list of Pharmaceutical Technology Europe’s top choices from the event’s educational agenda see ‘Editorial Educational Picks for Pharmapack 2020’ on PharmTech.com.)

With sustainability being a major global concern at the moment, the second session of the two-day educational conference will undoubtedly prove popular for those attending. Demand from drug retailers, hospitals, patients, and so on, is driving pharmaceutical packaging companies to evaluate ways of improving sustainability within their processes. In addition to several presentations on the topic of sustainability, the Pharmapack Awards will once again pay homage to companies forging the way with holistic approaches to sustainability and recyclability of packaging through the Eco-Design award.

“This year’s Pharmapack agenda highlights what an interesting time it is for packaging and drug delivery, showcasing the full depth and breadth of developments anticipated in the upcoming year,” revealed Silvia Forroova, brand director at Pharmapack in an event press release (2). “Most excitingly, our speakers feature some of the industry’s most prominent experts, leading pharma companies and new start-ups delivering tomorrow’s vital innovations.”

Important information

Dates: Wednesday 5 February and Thursday 6 February 2020.
Hours: 09:00–18:00 (Wednesday), 09:00–17:00 (Thursday)
Website: www.pharmapackeurope.com
Metro Station: Porte de Versailles

References

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Professionals working in biopharma drug development and manufacturing are concerned about the size of their paychecks, but other factors—including challenging work, job security, and company stability—may be more important when making career change decisions. Insight provided by bio/pharma professionals from around the world responding to Pharmaceutical Technology Europe’s annual employment survey (1) indicates strong confidence in the bio/pharma industry (66% expect business improvement in 2020) and some confidence in prospects for their employer (52% expect business improvement in 2020). More than half of the respondents, however, expressed interest in seeking better opportunities beyond their current position. (See the infographics on pages 20–21 for an overview of survey results.)

Job insecurity, company restructuring, a lack of training, an unsatisfactory work/life balance, and uncertainty about the company’s performance or success were the top reasons for job dissatisfaction. Similar to previous surveys (2–3), more than half of all respondents said they would like to leave their jobs, given the opportunity; however, 58% said they do not expect to leave in the coming year.

More than 44% of 2019 respondents—compared with one-third in 2018—said they stayed with the same employer, on average, for five or fewer years. More than one-quarter of the respondents said they voluntarily changed jobs in the past two years. The reasons cited—with multiple choices allowed—were to pursue a better career opportunity (72.7%), find more challenging work (40%), or to seek a better work-life balance (32.7%).

Salary was the fifth most-cited single reason for job change, trailing work/life balance, professional advancement, intellectual challenge, and job security. Nearly two-thirds of the respondents were confident they could find a job similar to their current position, should they choose—or were forced—to find new employment.

In the past two years, nearly one-quarter of the respondents said their company experienced a merger or acquisition, up from 18.1% in the previous survey; an additional one-quarter of the respondents reported that their companies had been through a downsizing or restructuring. Nearly 20% said they left the company due to these changes.

Respondents suggest a positive market for job seekers; 36.8% of respondents said there are few qualified candidates for open scientific/technical positions, compared with 30.3% in 2018. A smaller percentage (28% in 2019 vs. 34.2% in 2018) said there were more qualified candidates than open positions.

The compensation factor
Salary ranked sixth on a list of 12 factors contributing to job satisfaction, up from ninth place in 2018, trailing factors such as challenging projects, intellectual stimulation, company’s potential for success, a good work/life balance, and supportive management as the “main reason I come to work.” Satisfaction with compensation has trended downward during the past few years. More than 39% said they were paid fairly or excessively in 2019, compared with 41% in 2018 and 46% in 2017. In 2019, more than 40% of those surveyed said their pay was at the low end of the salary range for their expertise and responsibility; 17.6% said they were paid below market value.

The number of people reporting salary increases was stagnant from 2018 (54.1%) to 2019 (55.4%), following a drop from nearly 63% in 2017.

Additional statistics and analysis can be found on www.PharmTech.com.

References
1. Pharmaceutical Technology, 2019
2. Pharmaceutical Technology, 2018
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Please rate your satisfaction with your current salary.

I am paid below market value, considering my level of expertise and responsibility. 17.6%  20.5%

I am paid within market value for my job function, but at the low end of the range, considering my level of expertise and responsibility. 40.9%  38.2%

I am paid fairly for my level of expertise and responsibility. 38.9%  39.2%

I am paid excessively for my level of expertise and responsibility. 2.6%  2.1%

How secure do you feel in your job compared with last year?

More secure now 30.6% 24.7%

Less secure now 30.6% 30.6%

No change 39.4% 44.7%
Bio/pharma workers contemplate job and career changes.

- **I would like to leave my job, given the opportunity.**
  - 2019: 21.2%
  - 2018: 24.9%
- **I do not expect to leave my job in the coming year.**
  - 2019: 20.1%
  - 2018: 21.7%
- **I would like to change careers and leave the bio/pharma industry.**
  - 2019: 36.5%
  - 2018: 21.7%

If it were necessary for you to change jobs this year, how would you assess the job market?

- **2019**
  - It would be straightforward to find a job comparable to the one I have now.
    - 24.3%
  - It would take a while, but I would be able to find a job comparable to the one I have now.
    - 24.9%
  - It would be straightforward to find a job, but it probably wouldn’t be as good as the one I have now.
    - 21.2%
  - I would have to search hard and be prepared to take what I could get.
    - 17.8%

- **2018**
  - It would be straightforward to find a job comparable to the one I have now.
    - 20.1%
  - It would take a while, but I would be able to find a job comparable to the one I have now.
    - 21.7%
  - It would be straightforward to find a job, but it probably wouldn’t be as good as the one I have now.
    - 36.5%
  - I would have to search hard and be prepared to take what I could get.
    - 12.2%

In your career, how long, on average, have you stayed with the same employer?

- Less than 2 years: 12.2%
- 3 to 5 years: 24.4%
- 6 to 10 years: 17.8%
- 11 to 20 years: 40.8%
- More than 20 years: 9.6%

Which statement best describes the job market for scientific or technical positions in bio/pharmaceutical development and manufacturing in your geographic area?

- Competition for open positions is strong.
  - 36.8%
- Competition for open positions is moderate.
  - 36.2%
- Employers compete for qualified candidates.
  - 28.0%
The global biologics market has experienced significant growth over recent years and, according to market research, is expected to continue to grow in the near future (1). Advancement of the sector is projected to be driven by an increase in prevalence of chronic conditions, technological advancements, mergers and acquisitions, more market approvals, and the development of more efficient biologics (1).

However, biologics raise unique challenges in formulation and development, not least as a result of the large size of the molecules but also due to other characteristics of the complex API. According to Fran DeGrazio, vice-president, Global Scientific Affairs and Technical Services, West Pharmaceutical Services, the size of biologic drug products is particularly challenging when approaching drug delivery. "To be most effective, biologics must typically be injected directly into the bloodstream," she says. "Additionally, biologics are sensitive to their environment and can easily aggregate or denature, leading to problems such as the formation of particles, which may then be injected into the patient."

"Biological molecules are not only larger in size but also more complex in structure when compared with small molecules," concurs Constança Cacela, director—RD Analytical Development, Hovione. "This structural complexity can lead to challenges in ensuring stability during processing and long-term, which may result in potential losses of activity and increased immunogenicity."

Circumventing phenomena, such as denaturation, aggregation, and other forms of structural change, are of key importance when processing and developing formulations with biological molecules, Cacela further explains. "These aspects of biologics are responsible for an increased difficulty, requiring advanced technical expertise," she says.

Administration: Moving from IV to SC?
When developing large-molecule formulations, and depending on the delivery route, there will be different challenges to address with implication on the respective excipient selection, explains Eunice Costa, director—RD Drug Product Development, Hovione. "For injectables, concentration and viscosity of subcutaneous formulations are the main points to address and optimize, whereas for oral enzymatic and acidic degradations low absorption needs to be addressed as well," she says. "Finally, for nasal, the challenge is mainly related with the low absorption while inhalation is targeting the lung."

There has been an upswing in the proportion of drugs in the pipeline to be administered via a subcutaneous (SC) delivery route, with biomolecules that are currently administered intravenously (IV) being formulated for SC instead. "Major issues associated with SC administration for biologics are the small volumes that require high concentrations of the API," Costa adds. "The need for high concentrations results in increases of viscosity and challenges in maintaining isotonicity of the liquid formulation as well as in preventing aggregation. Moreover, viscous formulations are difficult and painful to administer. Addressing these issues includes careful optimization of the excipients in the formulation."

For DeGrazio, there are multiple approaches available for developers of formulations to be administered subcutaneously. "One approach is through optimization of the drug formulation design," she asserts. "This can be accomplished using technologies that help the drug meet deliverability criteria for SC injections."

Another approach includes using a suitable delivery device. "An example of this approach may be drugs that are delivered to the patient through wearable injector devices," DeGrazio continues. "Typically, a combination of both formulation optimization, and an appropriate delivery device, facilitates the transition from IV administration to SC."

Alternative routes
The size of biologic drug products—ranging from 3000 atoms to more than 25,000 atoms—has meant that the
primary route of administration is via injection, states DeGrazio. "Size is a challenge for crossing the barriers into the body using other routes," she says. "The oral route is preferred for any drug product. However, due to the sensitive nature of active ingredients, they will not survive the acidic pH and digestive enzymes of the stomach. This would be just the initial challenge, the next would be absorption into the bloodstream."

However, there are several benefits in developing biologic formulations for alternative routes of administration, argues Cacela, with probably the most obvious one being improved patient adherence. "In the development pipeline, there are increasing programmes in the areas of oral, inhalation, and nasal, with the first one generally being considered as the optimal route," she says.

To overcome the enzymatic and pH-dependent degradation of drugs in the stomach, in addition to permeability issues and the potential for degradation via first pass metabolism, formulation strategies, such as enzymatic activity inhibitors, permeation enhancers, enteric coatings, and carrier molecules, can be employed, Costa reveals. "The increased focus on inhalation delivery reflects the benefits offered by this route of administration," Costa continues. "Delivery by inhalation bypasses the harsh conditions in the gastrointestinal tract, allowing the administration of lower doses with reduced side effects, particularly for respiratory drugs delivered directly to the site of action."

For systemic delivery, administering drugs to the lungs can also allow direct absorption into the bloodstream, leading to a more rapid onset of action, Costa explains. "The main challenges for inhalation include ensuring that the drug reaches the lung (e.g., delivery efficiency), a limited array of excipients available to interact and stabilize large molecules that are safe in the lung, as well as the lack of permeability to very large biomolecules," she says. "Overall strategies include optimal design of the inhaler device, study of the interactions between excipients and biomolecules, biomolecule engineering (e.g., fragmented antibodies, anticalins) with the purpose of maximizing efficiency."

Nasal delivery, historically, has tended to be used for local delivery of drug substances. However, Costa adds that more recently it is becoming recognized as an interesting route for direct access to the brain. "It has been actively pursued for biologics, in particular peptides, due to the ease of administration," she states. "As opposed to inhalation, one of the major limitations of this route is the relatively limited low surface area available for absorption. To increase absorption, mucoadhesive polymers are commonly added to the formulation."

Cacela emphasizes that an overarching technological solution, useful for overcoming the limitations for the various delivery routes discussed, is the use of particle engineering. "Through the preparation of optimally sized and shaped particles, the..."
bioavailability of the drug can be improved,” she says. “As an example, nanoparticle-based delivery systems, such as lipid nanoparticles, are used for improving penetration of large molecules. In addition, these systems provide protection to the drugs, which is particularly relevant for large molecules administered orally.”

A common technique used to engineer particles is spray drying, which Cacela states is the most commercially advanced solution capable of preparing stable and effective formulations. “Despite being generally used for oral small molecules, its benefits can be easily expanded to other systems and routes of administration,” she adds. “The anticipated forecast growth for spray drying services being applied to biologics is a strong indicator of that (2).”

**Reformulation and self-administration trends**

SC administration of biologics, in particular antibodies, is a strategy being employed by industry to improve patient comfort and provide pharmacoeconomic benefits (3), highlights Cacela. Highlighting another example (4), she adds that in some cases using SC administration can result in improved safety due to reduced adverse effects. “Besides the aforementioned benefits, reformulation of existing biologics may also be of potential value for the originators as a means of life-cycle managements,” she says.

In agreement, DeGrazio notes, “We are definitely seeing the trend towards reformulation as part of lifecycle management to enable self-administration. New biologic drug products in competitive therapeutic categories are being introduced in self-administration systems. This is one of the main reasons for the growth of drug-device combination products in the marketplace.”

The move toward self-administration is being driven by a number of factors, DeGrazio continues. “One of the most significant is the potential cost savings if the delivery of a drug product can be done at home, versus in a hospital or clinic,” she says. “Additional reasons include improved quality of life for patients and product differentiation in a therapeutic category.”

**Mitigate risks, save costs**

The costs associated with any medical therapy are being scrutinized by regulatory bodies, governments, and patients. Biological therapies, due to the molecular complexity and associated challenges during development means that they come with a high price tag. “One of the best ways to impact costs is by mitigating risks early in the development process,” asserts DeGrazio. “Many drug product formulators think that all problems can be solved through their ability to adjust and optimize a formulation. However, not all formulators have a broad understanding of the impact of aspects beyond the drug formulation, aspects of which they need to be cognizant.”

Highlighting some examples, DeGrazio notes that formulators must be aware of the potential impact primary packaging may have on the biological drug product. Additionally, whether or not it is possible to use the drug product with a delivery device is an important consideration. “Both packaging and device options are essential when looking at improving the patient experience,” she adds. “The route chosen regarding drug pricing must not inhibit innovation and must ensure economic sustainability,” warns Cacela. “However, R&D effectiveness may be improved and, therefore, have an impact on the final cost of biologics.”

To improve R&D effectiveness, Costa explains that industry is using many different approaches. “Approaches such as preclinical models that more closely resemble the human conditions to be treated, reducing late-stage (Phase II and III) attrition rates and cycle times during development by using a better model,” she says. “New tools and technologies arising from the digital transformation era, such as the application of artificial intelligence algorithms to experimental and clinical data, further improve R&D effectiveness.”

Specifically looking at formulation, Costa reveals, “As more biomolecules are screened, models can be improved allowing for *in-silico* screening and reducing the chances of failure later on in clinical development.”

**Still on a learning curve**

For Cacela there is still much to learn and more development required in both the delivery and formulation of biologics. “Besides this, the diversity of these drugs and therapies is very large, and it is difficult to find a common solution even within a same class of biomolecules,” she states. “Therefore, the coming years will be marked by advances in the delivery of novel biologics, as well as biosimilars, with new solutions, new excipients, and new delivery support molecules.”

“We have learned that the drug formulation itself can have a detrimental impact on the function of a delivery device, such as a prefilled syringe system,” adds DeGrazio. “By understanding issues early in the development process, however, downstream problems can be avoided. Partnership with suppliers who are familiar with such challenges can be of great benefit. An openness to engage, and learn from each other, can benefit effective drug development and the patient.”

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Cetirizine dihydrochloride (CTZ) is a second-generation piperazine derivative, a potent H1 selective antihistaminic agent. Its extreme bitter taste results in poor patient compliance. The aim of this study was to prepare taste-masked drug-resin complex (DRC) using ion exchange resin Kyron T-134. The DRC was evaluated for effect of variables such as resin ratio, pH, temperature, soaking time of resin, and stirring time on drug loading and taste. Reconstitutable suspension was prepared using drug-resin complex and other pharmaceutical excipients in suspension. Formulated reconstitutable suspension was evaluated for parameters before reconstitution, such as flow properties and drug content, and after reconstitution, such as aesthetic appeal, sedimentation rate, redispersibility, particle size, viscosity, pH, drug content, and in-vitro dissolution study. During the evaluation period of 14 days, no significant change was observed in pH, viscosity, particle size, and drug content. From the results, it is concluded that effective taste masking of CTZ was achieved using Kyron T-134 and successfully evaluated in reconstitutable suspension.

A pharmaceutical suspension is a coarse dispersion in which insoluble solid particles are dispersed in a liquid medium (1). The US Food and Drug Administration’s (FDA’s) Center for Drug Evaluation and Research (CDER) denotes reconstitutable suspension as “Powder, For Suspension”, defined as an intimate mixture of dry, finely divided drugs and/or chemicals, which, upon the addition of suitable vehicles, yields a suspension (2). Reconstitutable suspension is reconstituted at the time of use and thus can be used as liquid formulation, which avoids swallowing problems. In aqueous solutions, many drugs degrade. Moreover, liquid product stability in tropical countries poses a great challenge because these products are exposed to elevated temperatures (up to 40 °C) and high relative humidity (up to 90%), especially during transport and storage (3,4).

Cetirizine dihydrochloride (CTZ) has a bitter taste and is prescribed extensively in both solid and liquid dosage forms for treating allergic conditions, including rhinitis and chronic urticarial (5). Its extreme bitter taste results in poor patient compliance in paediatric and geriatric patients. For these patients, drugs are commonly provided in liquid dosage forms, such as solutions, emulsions, and suspensions (6).

Ion exchange resins are solid and suitably insolubilized high molecular weight polyelectrolytes that can exchange their mobile ions of equal charge with the surrounding medium reversibly and stochiometrically. They are available in desired size ranges. Bitter cationic drugs can get adsorbed onto the weak cation exchange resins of carboxylic acid to functionally form a complex that is non-bitter. Further, resinates can be formulated as lozenges, chewing gum, suspension, or dispersible tablets and can mask the taste (7,8). Drugs can be bound to the resin by either repeated exposure to or prolonged contact with the resin. Drugs are attached to oppositely charged resin substrates or resinates through weak ionic bonding so that dissociation of the drug-resin complex (DRC) does not occur under salivary pH condi-


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PharmTech.com
tions. This suitably masks the unpleasant taste and odour of drugs (9). The objective of this study was to mask the bitter taste of CTZ using ion exchange resin Kyron T-134 and check the feasibility of incorporating the DRC into reconstitutable suspension to increase patient compliance.

Materials and method

**Materials.** CTZ was received from UCB India Private Limited (Vapi, India). The resin, Kyron T-134 (Batch no. 3009022), was procured from Corel Pharmachem (Ahmadabad, India). Xanthan gum, microcrystalline cellulose PH101, aspartame, sucrose, propyl paraben, and orange dry flavour were obtained from S.D. Fine Chemicals, Mumbai, India. Deionized distilled water was used throughout the study.

**Preparation of DRC.** DRCs were prepared by reacting CTZ with cation exchange resin Kyron T-134 in various stoichiometric ratios (1:1, 1:2, 1:3, 1:4, and 1:5). Kyron T-134 as weight ratio of the drug was placed in a beaker containing a required quantity of deionized water and allowed to swell. Accurately weighed CTZ was added to the solution and stirred. The mixture was filtered using Whatman filter paper, and residue was washed three times with 75-mL deionized water each time and dried. Drug in complex was calculated as drug-loading efficiency. DRC was optimized for various process conditions like drug-to-resin ratio, effect of pH, effect of temperature, effect of soaking time of resin, and effect of stirring time (8,10).

**Evaluation of DRC

**Percentage yield.** Percentage yield of DRC was calculated by practical yield divided by actual theoretical yield (11).

**Drug content.** The CTZ content was determined by dissolving 100 mg of DRC with continuous stirring in 100 mL 0.1 N hydrochloric acid (HCl) (pH 1.2) for 4 h. The solution was filtered. After suitable dilution, the drug content was determined as drug-loading efficiency. DRC was optimized for various process conditions like drug-to-resin ratio, effect of pH, effect of temperature, effect of soaking time of resin, and effect of stirring time (8,10).

**Physical properties of DRC.** Physical properties of DRC, such as particle size, angle of repose, bulk density, tapped density, compressibility index, and Hausner’s ratio were determined. All parameters were performed in triplicate (12,13).

**In-vitro drug release study.** Drug release from DRC (optimized drug: resin ratio of 1:3.5) in 0.1 N HCl was determined using a United States Pharmacopeia (USP) XXIV type II (paddle type) dissolution apparatus. DRC equivalent to 10 mg of drug was weighed accurately and added to 900 mL 0.1 N HCl and maintained at 37 °C. Drug release was performed at 100 rpm for 30 min. Five-milliliter samples were withdrawn after every five minutes up to 30 minutes. Samples were filtered with Whatman filter paper no. 41 and were analyzed at 231.5 nm by UV/Vis (12). The readings were taken in triplicate.

**Characterization of DRC

**Infrared study.** The drug, resin, and DRC were subjected to Fourier transform infrared (FTIR) studies to check any drug–resin interaction. FTIR spectra were recorded on samples prepared in potassium bromide using FTIR-8400S with infrared (IR) solution software (Shimadzu, Germany). Data were collected over a spectral region from 4000 cm⁻¹ to 400 cm⁻¹ (11).

**Preparation of oral reconstitutable suspension.** The oral reconstitutable suspension of CTZ was prepared from the optimized DRC. The formula is presented in Table I. All the ingredients for suspension were sieved through mesh no. 40 to make uniform particle size dispersion. The DRC equivalent to 10 mg/5 mL of CTZ was added to the suspension. They were mixed properly to ensure uniform dispersion. Evaluation was performed on parameters before and after reconstitution (14,15).

**Evaluation of oral reconstitutable suspension.** Dry powder blend, ready for reconstitution, was evaluated for flow properties and drug content. After reconstitution, different parameters, such as sedimentation volume, redispersibility of suspension, viscosity, pH, drug content, and in-vitro drug release study were evaluated (10,16).

**Sedimentation volume and redispersibility of suspension.** The formulated suspension was evaluated for physical stability by determining the sedimentation volume. Fifty milliliters of suspension was taken in a 100-mL stoppered graduated measuring cylinder. The suspension was dispersed thor-

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**Table I. Formulation of cetirizine dihydrochloride (CTZ) oral reconstitutable suspension.**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Functional category</th>
<th>mg/5 mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-resin complex (equivalent to 10mg/5 mL of CTZ)</td>
<td>Taste-masking drug</td>
<td>55</td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>Suspending agent</td>
<td>30</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>Suspending agent</td>
<td>30</td>
</tr>
<tr>
<td>Propyl paraben</td>
<td>Preservative</td>
<td>20</td>
</tr>
<tr>
<td>Orange flavour</td>
<td>Flavour</td>
<td>25</td>
</tr>
<tr>
<td>Titanium dioxide</td>
<td>Opacifier</td>
<td>12</td>
</tr>
<tr>
<td>Sucrose</td>
<td>Filler</td>
<td>50</td>
</tr>
</tbody>
</table>
oughly by turning the measuring cylinder upside down three times. Later, the suspension was allowed to settle for three minutes, and the volume of sediment was noted. This is the original volume of sediment (H0). The cylinder was kept undisturbed for 14 days. The volume of sediment was read at day 0, at day 7, and at day 14. The day 14 reading was considered the final volume of sediment (Hu) (Equation 2).

\[
\text{Sedimentation volume} = \frac{H_u}{H_0}
\]  

\[\text{Eq.2}\]

**Determination of viscosity.** A viscosity study was performed using a Brookfield viscometer DV-II+Pro, USA (Spindle no. S61). Viscosity was measured at 100 rpm, at 25 °C. The limits on viscosity were selected such that the suspension reached a physically stable state.

**pH of the suspension.** pH of the suspension was determined using a digital pH meter.

**Assay of suspension.** Five milliliters of suspension were taken in a 50-mL volumetric flask, and the volume brought up to 50 mL with 0.1 N HCL. The solution was sonicated for 30 min and filtered. Absorbance was then measured at wavelength 231.5 nm in UV-Vis, after which the percentage drug content was calculated.

**In-vitro drug release.** In-vitro drug release of the suspension was performed using USP-type II dissolution apparatus (paddle type). The dissolution medium of 500 mL 0.1 N HCL was placed into the dissolution flask and temperature was maintained at 37±0.5 °C at 100 rpm. Five milliliters of suspension solution was placed in each flask of the dissolution apparatus. The apparatus was allowed to run for 35 minutes. Samples measuring 10 mL were drawn after every 5 min, 10 min, 15 min, 20 min, 25 min, 30 min, and 35 min. The fresh dissolution medium was replaced every time with the same quantity of the sample. Collected samples were suitably diluted with 0.1 N HCL and analyzed at 231.5 nm using 0.1 N HCL as blank. The cumulative percentage drug release was calculated.

**Results and discussion**

**Drug loading.** As presented in Table II the complexation of drug with Kyron T-134 in a weight ratio of 1:3.5 gave efficient drug loading. The stirring time for all subsequent complexation processes was fixed to 4 h. Stirring time between 4 h and 5 h showed no significant change. The pH and temperature of solution did not show any significant effect on drug loading. Therefore, pH 4 and room temperature were selected for optimized batch preparation. No significant difference was observed when soaking time of resin in deionized water was changed from 30 min to 120 min. Thus, the soaking time of resin in deionized water was fixed to 30 min. Optimum conditions for the preparation of DRC were selected and used for further studies.

**Micromeritics.** The bulk and tapped densities were found at 0.613±0.013 and 0.674±0.016 g/cc, respectively. The compressibility between 5%-12% indicates excellent compressibility. The values of Hausner’s ratio at less than 1.25% and angle of repose below 30° indicates good flowability.

**In-vitro drug release from DRC.** Figure 1 demonstrates the drug release studies of CTZ from the DRC in 0.1 N HCL, phosphate buffer pH 6.8, and deionized water. In 0.1 N HCL more than 90% of drug release was achieved in 5 min, whereas in phosphate buffer pH 6.8 and deionized water, less than 20% drug release was achieved in 30 min. The exchange process of drug release is shown in Equation 3:

\[
\text{Resin} - \text{Drug}^+ + \text{X}^+ \rightarrow \text{Resin} - \text{X}^+ + \text{Drug}^+
\]  

\[\text{Eq.3}\]
Where $X^+$ represents the ions in the gastrointestinal tract.

The presence of $H^+$ ion in the 0.1 N HCl results in the displacement of CTZ, thus facilitating drug release. The amount of drug released was insufficient to impart a bitter taste in deionized water and phosphate buffer pH 6.8.

**Characterization of DRC**

**FTIR spectroscopy.** The complexation was confirmed by IR studies. The absence of peaks at 2323 cm$^{-1}$–3046 cm$^{-1}$ and at 1741 cm$^{-1}$ in DRC denotes complexation of drug and resin. The IR spectra of complex showed that there was no observed incompatibility between drug and resin. Peaks of both drug and resin were observed and interpreted (Figure 2).

**Reconstituted suspension.** Prepared suspension was evaluated for flow properties and drug content before reconstitution. Results are shown in Table III. Results showed that the reconstitutable blend has excellent flow properties and optimum drug content, and that the prepared blend had good dispersion homogeneity. At the time of use, the reconstitutable blend was reconstituted with water for preparation of suspension.

**Sedimentation volume of suspension.** The ultimate height of the solid phase after settling depends on the concentration of solid and the particle size. In prepared formulation, there was little sedimentation after 7 days and 14 days, and the particles could be easily redispersed. Moreover, uniform dispersion was achieved after a minimum number of strokes. Results are shown in Table IV.

**Sedimentation volume**

<table>
<thead>
<tr>
<th>Test</th>
<th>$H_u$</th>
<th>$H_0$</th>
<th>Sedimentation volume ($H_u/H_0$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 h</td>
<td>48</td>
<td>50</td>
<td>0.96</td>
</tr>
<tr>
<td>7 days</td>
<td>40</td>
<td>50</td>
<td>0.8</td>
</tr>
<tr>
<td>Hauser’s ratio</td>
<td>32</td>
<td>50</td>
<td>0.64</td>
</tr>
</tbody>
</table>

**Angle of repose (°) 29.56**

**Drug content (%) 98.26±0.526**

**Table IV. Sedimentation study of suspension.** $H_u$ is sedimentation volume at 14th day. $H_0$ is original sedimentation volume at 0 day.

**Table V. Evaluation parameters of after-reconstitution oral suspension.**

<table>
<thead>
<tr>
<th>Sample no.</th>
<th>Test</th>
<th>0 day</th>
<th>7 days</th>
<th>14 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Appearance</td>
<td>Uniform</td>
<td>Uniform</td>
<td>Uniform</td>
</tr>
<tr>
<td>2</td>
<td>Taste</td>
<td>Uniform</td>
<td>Uniform</td>
<td>Uniform</td>
</tr>
<tr>
<td>3</td>
<td>pH</td>
<td>6.8±0.1</td>
<td>6.7±0.1</td>
<td>6.7±0.1</td>
</tr>
<tr>
<td>4</td>
<td>Viscosity (cps)</td>
<td>56</td>
<td>52</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>Particle size</td>
<td>265±55</td>
<td>268±45</td>
<td>272±48</td>
</tr>
<tr>
<td>6</td>
<td>Drug content</td>
<td>98.45±0.521</td>
<td>98.012±0.865</td>
<td>98.32±0.601</td>
</tr>
</tbody>
</table>

**Figure 2. Fourier Transform infrared spectra of (a) cetirizine dihydrochloride, (b) Kyron T-134, and (c) drug-resin complex.**
reconstitution. There was no appreciable change observed in pH and drug content. Size of the particles in suspension was reasonably constant even after 14 days. This indicated no crystal growth. Results are shown in Table V.

**In-vitro drug release.** Drug release from the prepared formulation was observed in 0.1 N HCl. Results showed that nearly 85% of drug release was found from prepared suspension in duration of 5 minutes. This is happened because drug in form of DRC is weak enough to be broken down at gastric pH 1.2 and allow the rapid release of drug from suspension.

**Conclusion**

In the present study, an attempt was made to mask the bitter taste of CTZ by using Kyron T-134 as an ion exchange resin. Various parameters affecting taste masking, such as resin ratio, pH, temp, soaking time of resin, and stirring time were optimized with efficient loading of drug. The nature of the DRC is such that the average pH of 6.8 in saliva is not able to break the complex. In-vitro drug release in salivary pH of 6.8 was less than 5% within 60 s. Ideally, an oral suspension is swallowed by a patient in a fraction of that time (not more than 60 s). Yet, the DRC is weak enough to be broken down at gastric pH 1.2, thus the complex is considered absolutely tasteless in salivary fluid. Taste-masked DRC has shown excellent flow properties in this study. Furthermore, formulated CTZ reconstitutable suspension has acceptable sedimentation properties. In a 14-day evaluation period, it is observed that no significant change was observed in pH, viscosity, particle size, and drug content. This method is simple and cost effective to prepare taste-masked reconstitutable suspension of CTZ that may be acceptable to the industry industry.

**References**

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Self-Guided Control of a Fluid Bed Granulation Process

Advanced dynamic process control using PAT data improves product quality.

Globally, there is an increasing trend toward the use of Industry 4.0 principles, with the Industrial Internet of Things (IIoT) being a key component, while regulators are actively encouraging pharmaceutical companies to modernize their approaches to drug development and manufacturing to deliver higher quality products. Better process understanding, drug product development, and manufacturing throughout the commercial lifecycle of drug products will lead to faster time-to-market and a more reliable, predictable supply chain (1).

Adopting several of the tools and technologies which are part of the current Industry 4.0 revolution (e.g., process analytical technology [PAT], big data analytics, manufacturing intelligence, in-process control, and cloud architecture) into everyday pharmaceutical product development and commercial manufacturing may provide an effective solution to many manufacturing quality challenges. Adoption of these technologies would also dramatically improve productivity while maintaining competitive advantage and reducing costs for the manufacturer (2,3).

This article presents a practical application of Industry 4.0 architecture with commercially available technology solutions and demonstrates how the system can be implemented to reduce risks associated with traditional fluid-bed granulation manufacturing processes.

Fluid-bed wet granulation involves agglomerating a mix of dry primary powder particles (APIs and excipients) by the addition of a granulating solution in a fluid-bed granulator. In the subsequent drying phase, control is crucial because over-drying can lead to increased attrition and fracture of the product, while insufficient drying can result in bed stalling, poor flow, and product stability issues (4). The traditional control approach is recipe driven and largely operator dependent, with minimal provisions for the impacts of raw material or atmospheric variations, both of which are known to affect final granule properties (5).

The automated approach described in this article resulted in greater in-process control and repeatability as well as less batch-to-batch variation. The controller design presented here is intended as a novel example to highlight the flexibility and potential when developing this type of automated, control-driven approach.

Materials and equipment

Formulation. A placebo formulation was used for all batches. It consisted of a mixture of lactose (1 kg Pharmatose 200M, DFE Pharma) and microcrystalline cellulose (0.5 kg AvicelPH-101 NF, DuPont). The liquid binder was an aqueous solution of polyvinylpyrrolidone (1 L, 5.8% w/w, Plasdone K-90, Ashland). Materials were supplied by IMCD Ireland.

Process equipment. Fluid bed granulation was performed in a granulator (Glatt GPCG2) equipped with a particle analyzer (Eyecon2, Innopharma Technology) and near infrared (NIR) spectrophotometer (Multieye2, Innopharma Technology) measuring particle size distribution and product moisture content, respectively. The equipment is shown in Figure 1. The automated process control platform (SmartX, Innopharma Technology) provided time-aligned data aggregation of process parameter data, PAT data, and environmental sensor data.

Controller development

Controller development is complex and requires a thorough understanding of the process, including critical process parameters (CPPs), their impact on critical quality attributes (CQAs), and the required process specifications. In this case, information on the process design space and optimum control was derived from retrospective analysis of more than 160 batches run on the test-bed system (SmartX Innopharma Technology), while further detailed experimentation was performed to quantify the differences in end-product quality between the results of this advanced dynamic process control
Manufacturing

(ADPC) approach and the results using a traditional control approach.

The first step in the development was to clearly define the control logic for each process phase. This included identification of key dynamic control relationships, establishing fixed setpoints as well as phase and process endpoint criteria. Once configured, this flexible control logic was then implemented and executed via a process-centric scripting environment within the integrated ADPC module. Throughout the process, real-time PAT data and process sensor data from the fluid-bed system and environmental systems provided a continual input feed to the controller. The controller used this information to make scenario-based decisions on how to respond to process deviations as well as required process changes, including phase changes and endpoint detection.

For the ADPC example presented in this article, five process phases were defined: empty heating, material heating, spraying I, spraying II, and final drying. Figure 2 describes the five process phases and their corresponding key set-points and endpoint criteria.

Spraying is divided into two phases to demonstrate how PAT measurements may be implemented to achieve in-process control. Additionally, the two phases are designed with the intention to help mitigate against product attrition as typically observed during final drying, thus delivering more consistent endpoint particle size with less batch-to-batch variation. Spraying I is defined by rapid wetting and maximum growth, while Spraying II is defined by further hardening of the granules through reduced spray rate and increased moisture removal to mitigate against product attrition during the drying phase.

A specific moisture-content reduction rate was empirically determined to achieve a quasi-stable median volume distribution ($D_{50}$) particle size while allowing for faster control reaction and, therefore, minimized process deviations as
compared to controlling directly based on particle size.

**Results and discussion**

**ADPC controller.** The series of CQA and CPP profiles shown in Figure 3 are taken from one of the fluid-bed granulation processes executed by the ADPC controller that was developed; these profiles demonstrate the control method’s capabilities.

**Dynamic control relationships.** The key relationship between spray rate and Dv50 particle size can be observed between Figure 3a and 3c. The controller sets the Dv50 particle size target to 450 µm for the duration of spraying and uses real-time particle size data, as measured by the Eyecon, to monitor the growth profile. During Spraying I, a fixed spray rate is maintained for rapid moisture addition and growth until the target particle size is reached. On entering Spraying II, the target particle size is maintained by following the empirical target moisture-content profile.

This profile is maintained by dynamic control of the spray rate based on real-time moisture content data. Comparing Figure 3b and 3c, modulation of the spray rate after a brief delay can be observed in response to small deviations of the moisture content trend either above or below the target moisture content profile (Figure 3b, dashed line labelled ideal moisture overlay). This process slowly dries the granulate to 5%, which is the trigger to transition to the final drying phase.

Another novel aspect of this control approach can be observed in Figure 3b, where the effect of linking air flow rate to moisture content during the Spraying I phase can be seen. This approach allows optimum fluidization to be maintained while the bed becomes heavier and more cohesive, avoiding both the attrition and efficiency impacts of over-fluidizing, and the under-fluidizing risk of bed-stalling.

**End-product quality.** Endpoint Dv50 particle size values from a number of granulation batches manufactured with the ADPC controller were compared to the endpoint Dv50 particle size values from earlier batches manufactured using a non-ADPC controlled, recipe-driven approach. A significant difference in endpoint product consistency is apparent between the two approaches.

---

**Figure 3.** Advanced dynamic process control controller process profiles. NIR is near infrared spectrophotometer; Dv10, Dv50, and Dv90 are volume-based particle-size distributions containing 10, 50, and 90% respectively.
Comparing batches manufactured with the ADPC controller, a tighter distribution in endpoint Dv50 particle size values is evident, with variation of only 46 µm reported from smallest to largest Dv50 value. These results demonstrate the consistency in batch-to-batch particle size that can be achieved by implementing such a control approach within a fluid-bed granulation process. The ability to achieve greater particle size control via the ADPC controller approach leads to more consistent endpoint particle size and less variation between batches.

Figure 4a illustrates a significantly wider distribution of endpoint Dv50 particle sizes for batches manufactured via the non-ADPC controlled approach, with variation of 171 µm from the smallest to largest Dv50 value. Comparing batches manufactured with the ADPC controller, a tighter distribution in endpoint Dv50 particle size values is evident, with variation of only 46 µm reported from smallest to largest Dv50 value. These results demonstrate the consistency in batch-to-batch particle size that can be achieved by implementing such a control approach within a fluid-bed granulation process. The ability to achieve greater particle size control via the ADPC controller approach leads to more consistent endpoint particle size and less variation between batches.

Figure 4b clearly demonstrates this variation with a much wider distribution of final LOD values evident for the non-ADPC controlled batches. The total spread of moisture content values is 0.48% for these batches, compared to only 0.16% for the ADPC-controlled batches, which demonstrate much tighter control. These results demonstrate the benefit of the in-line NIR moisture-content endpoint detection method. Endpoint moisture content of the fluid bed granulation process is critical to final product quality and process performance and must be tightly controlled to avoid issues with downstream processing, product dissolution, and stability as well as drug absorption rates in the body. Implementing an ADPC approach can reduce batch-to-batch variation and improve batch repeatability and quality.

Conclusion

The ADPC-controlled approach to fluid bed granulation was shown to produce more consistently sized granules with less batch-to-batch variation when compared to granules produced from a non-ADPC controlled process. In addition, endpoint LOD analysis for the ADPC batches showed significantly less variation and greater consistency. Overall, high process repeatability and reproducibility were demonstrated across multiple, successfully manufactured fluid-bed granulation batches.

The real-time measurements of particle size and moisture content allowed the ADPC controller to effectively determine phase-end criteria. It was further shown to be possible to dynamically manage spray rate, thus ensuring a predetermined moisture content profile was followed by leveraging the NIR moisture-content data.

Finally, the addition of PAT and its integration into the process control strategy dramatically reduces the need for at-line sampling and testing associated with more traditional granulation approaches, as well as reducing the risks associated with human error.

References

Performing equipment maintenance to prevent breakdowns or unplanned process stops is an obvious best practice; how to know when to do that maintenance is not as simple. Preventive maintenance is the conventional pharmaceutical industry practice that involves setting a time-based maintenance schedule for a piece of equipment, typically using models based on experience and original equipment manufacturer (OEM) recommendations. Preventive maintenance schedules are usually set conservatively, to be short enough to have a low risk of failure.

Digital tools are helpful in managing this routine and scheduled maintenance. “Many companies still rely on paper records to manage their manufacturing floors, including equipment maintenance activities. But in a high-paced and high-volume production environment, you simply can’t be proactive when you operate on paper,” suggests Matt Lowe, MasterControl’s president of laboratories. “Digital preventive maintenance systems are the bare minimum in today’s competitive manufacturing marketplace. The goal is to avoid missed or delayed maintenance tasks and keep equipment in good working condition,” says Lowe.

Some pharmaceutical manufacturing facilities run 24 hours a day, seven days a week, with two-week shutdowns twice a year for preventive checks, notes Jon Biagiotti, product marketing manager at Augury. This standard approach, however, may not be cost-effective or an optimal use of resources. “Preventive maintenance may be done too late, not addressing potential issues until the next scheduled check, so that it degrades to a more expensive fix. Or it may be done too early, when it isn’t needed yet,” he says.

“The pharmaceutical community is showing great interest in predictive maintenance because the conservative nature of our applications results in frequent preventive maintenance. Preventive maintenance is not always needed and results in costly downtime,” adds Pamela Docherty, industry manager at Siemens.

Continuous monitoring and condition-based predictive maintenance offer the potential to improve efficiency and quality compared to time-based preventive maintenance.

**Predictive maintenance**

Predictive maintenance takes asset health analysis to the next level, by collecting data from equipment using sensors connected through the Industrial Internet of Things (IIoT) and analyzing that data to predict how an asset will perform in the future. Decisions are tailored for a specific situation, rather than following a general expectation.

“In the past, predictive analytics on a set of many assets was too time consuming to be practical, but advanced analytics enables faster, cost-effective insights,” explains Michael Risse, vice-president and chief marketing officer at Seeq. Using the IIoT and predictive analytics, “the assets that need attention provide advanced warning on what they will need in terms of spare parts and maintenance in enough time to take action at the best price and timing for the organization.” In many cases, data needed for predictive analytics are already collected and available in historians or other databases, says Risse. If more data are needed, sensors and wireless networks are easily added. The barrier to predictive maintenance is, thus, not the availability of data, but the ability of subject matter experts to leverage the data. “It’s the ability to create actionable insights and deliver it through an easy-to-use interface that creates value,” notes Risse.

Enabling process engineers to analyze the data themselves, with self-service analytics, gives these experts the knowledge they need to optimize maintenance, says Edwin van Dijk, vice-president of marketing at TrendMiner. Another key to self-service analytics is contextualizing the data coming from the equipment using process-related data. “The goal of predictive maintenance is to be able to perform
maintenance at a time when it is not only the most cost-effective, but also when it will have the least impact on operations,” says van Dijk.

“Human intervention is critical to determine the best course of action based on the available information,” adds Lowe. For example, with insight into an upcoming problem, “manufacturers can proactively reassign equipment and divert upcoming batches to other production lines.”

### Machine learning

Advances in computing power and in artificial intelligence (AI)—particularly machine learning—have enabled predictive maintenance. For example, digital twin libraries (i.e., collections of models) were originally developed by OEMs for specific equipment, and now general models that can be tuned to specific pieces of equipment are increasingly available, says Elinor Price, senior product manager at Honeywell Process Solutions. She says that the role of the asset digital twin is to alert the maintenance team to be proactive rather than reactive. For example, advanced pattern recognition analytics (i.e., machine learning) can identify potential equipment problems by spotting changes in flow or temperature before they are large enough to trigger an alarm on the control system.

“Machine learning algorithms build a model of the machine to learn how it operates,” explains Biagiotti. “By comparing current performance to past performance, anomalies can be detected. Full fault diagnostics can be conducted by looking at the frequency spectrum, applying pattern recognition, and comparing signals to similar machines. Based on [these diagnostics], specific, actionable recommendations are made to improve the health of a machine.” Machine learning is often based on vibration analysis, but it goes beyond a conventional rules-based system. “The system learns how the machine operates so that you don’t receive false alarms,” says Biagiotti. “By comparing one machine’s data to similar machines, the accuracy improves exponentially as we collect more data. Because the IoT is being leveraged, manufacturers can benchmark equipment and production lines at a global level, comparing plants around the world.”

### Use cases

Biagiotti says that one of the main uses of machine learning algorithms is monitoring cleanroom utilities, where shutdowns result in the time-consuming and expensive process of reconditioning the cleanroom. Air-handling units, for example, are usually enclosed and difficult to access, but wireless sensors can be placed in the enclosure to send data through the IoT. In one case, machine learning algorithms identified bearing wear on two air handling units, and correcting the problem prevented an unexpected shutdown.

In another case, vibration analysis was used to detect misalignment and bearing failure on a chilled water system pump. The pump was required to keep a constant temperature for experimental product. “The system detected a failure 120 days in advance, saving batch experiments that, if lost, could have wasted months of time,” says Dennis Belanger, director of Operational Certainty Consulting at Emerson.

He reports on another use, “Emerson worked with one organization to develop a machine learning system that could detect sensor drift on a temperature sensor for a heat-treatment enclosure to send data through the IoT. That implementation detected an aberration 60 days in advance, which allowed the organization to save a batch worth over US$1 million.”

Heat-exchanger performance is crucial for process control and offers an opportunity for maintenance optimization, says van Dijk. “ Fouling of heat exchangers increases the cooling time, but scheduling maintenance too early leads to unwarranted downtime. Scheduling too late leads to degraded performance, increased energy consumption, and potential risks,” he explains. “In a reactor with subsequent heating and cooling phases, the controlled cooling phase is the most time-consuming, and it is almost impossible to monitor fouling when the reactor is used for different product grades and when a different recipe is required for each grade. In one instance, a monitor was set up to look at the cooling times of a company’s most highly produced products. If the duration of the cooling phase started

### Design for reliability

Design for reliability (DFR) is a methodology for ensuring that equipment or other assets are built so that they run consistently without unexpected failure, and that they can be accessed and maintained over time. “Asset health accountability drives the creation and execution of a robust reliability framework,” says John Ganaway, Design for Reliability practitioner at Jacobs. Software may assist in DFR, but in reality it is the stakeholders who must “build and execute a reliability framework,” says Ganaway. Pharmaceutical Technology Europe interviewed Ganaway about DFR and its application in pharmaceutical manufacturing.

**PTE: How do new technologies such as AI/predictive maintenance aid in DFR?**

**Ganaway (Jacobs):** System health indicators (SHIs) are crucial. They are based on such process health indicators (PHIs) as pH, conductivity, pressure, temperature, and flow, and then integrated with asset health indicators (AHIs) (e.g., vibration magnitude with frequencies, oil cleanliness such as ISO codes, temperature using thermography, ultrasound using acoustics, current, voltage, and material thickness). With these data, artificial intelligence (AI), using improved data models, can create a method for enumerating defects. Once users are aware of the defects and the probability of their occurring, they can make better design decisions, eliminating those defects at the design stage.

To read the full interview, go to [www.PharmTech.com/designing-pharma-equipment-reliability](http://www.PharmTech.com/designing-pharma-equipment-reliability)
to increase, a warning was sent to the engineers who could then schedule timely maintenance, sometimes two to three weeks in advance. The gained benefits are extended asset availability, predictive maintenance leading to operational and maintenance cost reduction, and reduction of safety risk.”

Predictive algorithms can also prevent the breakthrough of a filter in a suspension tank, which is used for removing impurities in a product before it is fed into the batch. “Sometimes one of the valves can leak, and gas can enter the system. But sometimes the valve can really be stuck due to solids, and the pressure keeps on building up until the filter eventually breaks,” notes van Dijk. “Using self-service analytics, process engineers set up the monitors to identify when the valves were leaking, which could be an early indicator of a filter breakthrough that could contaminate an entire batch. With the predictive monitors, the equipment can be replaced sooner, or the process can be controlled differently.”

Belanger concludes, “What all successful examples have in common is that decision makers closely examine critical points of failure in the organization and developed solutions that gave the organization the time it needed to react efficiently but thoughtfully, to drive more positive outcomes overall.”

Prescriptive maintenance
Prescriptive maintenance is a new term to describe a method for automatically scheduling required maintenance based on predictive algorithms. “This type of maintenance requires even more data from many more sources than the ‘few’ sensors at the equipment. Operational contextual information is required to artificially assess all circumstances to generate the adequate prescription for the maintenance required,” explains van Dijk.

“Prescriptive maintenance is being adopted by best-in-class pharma manufacturers to drive better production through more informed decision making,” adds Belanger. He explains that this method uses analytics tools to “find patterns or anomalies in large amounts of seemingly unrelated data—understanding and evaluating the performance of a process or system rather than measuring the condition of a single piece of equipment.” A corrective action is then “prescribed” to minimize or prevent failure.

The pharmaceutical industry is not ready for a “fully artificial intelligence-led prescriptive analytics system for running an autonomous factory,” says van Dijk. “A human-interacted artificial intelligence system is currently a much safer bet.” In this system, the process engineers and operators use all the available information to create “process monitors.” These automated monitors send “prescriptions” for future maintenance action to the appropriate people or systems in the plant.

Data analysis methods
For both predictive and prescriptive maintenance, understanding the process, building data models, and analyzing the data are key, says Edwin van Dijk, vice-president of marketing at TrendMiner. Subject matter experts—the process engineers—can use “self-service analytics” tools to search and filter data, perform root cause analysis, test hypotheses, and build monitors to predict process and equipment performance. Van Dijk explained three ways to analyze data using this self-service analytics approach.

“The first is event-based. If a certain signature behaviour is detected that can affect another part in the process that typically occurs later, a notification can be generated. This notification can include instructions for the required preventive actions or required maintenance. The second is probabilistic. The current behaviour is interpreted, and a likeliness of future behaviour is calculated, optionally resulting in automatically scheduled maintenance work orders with the needed instructions. The third type is regressive. The prediction is based on certain conditions that must be met and verified, and in case of deviations, the instructions can be given to the control room, or maintenance can be scheduled for the near future. For all three situations, the events can be captured in case they occur, providing more information for improving future predictive and even prescriptive maintenance work.”

Implementation and data integrity
When getting started, companies should first analyze which data are already available and whether existing networks are adequate for data collection. If so, they should move forward with analyzing data, “find the low hanging fruit,” and use it to optimize maintenance activities, suggests Donald Mack, industry manager at Siemens.

Quality teams must be educated on the reliability of predictive maintenance, adds Docherty. “It is likely that companies will ‘watch’ the predictive maintenance data and get an understanding, while slowly pushing the time interval between each predictive maintenance,” she says.

Data integrity is crucial for IIoT-connected equipment. “Digitalization and cybersecurity go hand in hand. What were once isolated, nearly impossible to access devices are now being brought on to the information superhighway,” says Mack.

“A strong IIoT solution requires a detailed, security-driven system architecture that can effectively represent multi-layered security within the solution,” adds Brycen Spencer, IoT consultant at Siemens. “Companies should seek a solution designed to be scalable, resilient, and efficient. Features such as strict access management, encryption, network security, tenant and environment separation, and filtered communication channels are fundamental to good IIoT architecture.”
Gerresheimer

Company description
Gerresheimer is a leading global partner to the pharma and healthcare industry. With specialty glass and plastic products, the company contributes to health and well-being. Gerresheimer operates worldwide and its approximately 10,000 employees manufacture products in local markets, close to its customers. With plants in Europe, the Americas, and Asia, Gerresheimer generates revenues of around EUR 1.4 billion. The comprehensive product portfolio includes pharmaceutical packaging and products for the safe, simple administration of medicines: insulin pens, inhalers, micro pumps, prefillable syringes, injection vials, ampoules, bottles, and containers for liquid and solid medicines with closure and safety systems as well as packaging for the cosmetics industry.

Major products/services being exhibited
The Gx RTF injection vials are made from type I borosilicate glass and meet all current requirements of the applicable ISO standards and pharmacopoeias (USP and Ph. Eur.). They are manufactured in accordance with cGMP, washed in a cleanroom, packed in trays or in nests and tub and finally sterilized. Gerresheimer offers its own packaging as well as the well-known Omni EZ-fill packaging design. This means the vials are ready for the next steps in the filling process without any further and/or additional handling. The benefits are obvious: sterile delivery, a simplified fill-and-finish process, the highest quality standards, flexibility thanks to various possible packaging options and a wide range of filling and sealing technologies. These all lead to a significant reduction on overall manufacturing costs across the product’s entire lifecycle and improve patient safety.

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Stoelzle Glass Group

Company description
The Stoelzle Glass Group consists of six European production sites, two of them dedicated exclusively to glass containers for the pharma and healthcare sectors. Our success story has been written largely by a team of committed and motivated employees. Innovation and a strong customer focus, as well as sustainability and security are absolutely paramount in our production. We know precisely what goes into our glass and how it gets there, at all times, for the simple reason that we are scrupulous about monitoring the entire value creation chain. Thanks to sophisticated technologies, our glass containers are traceable and tamper-proof, so that our customers can fulfill their responsibility to the final consumer.

Major products/services being exhibited
Stoelzle bottles are part and parcel of the final medicine product—that’s why we place such great value on top-quality production. In no other sector is certified quality and reliability as vital as in medical products. Stoelzle manufactures soda lime Type III glass containers such as dropper bottles, medicine and syrup bottles, injection vials, infusion bottles, as well as tablet jars or wide mouth packers. Volumes range from 3.5 mL up to 1000 mL bottles. What distinguishes us from other glass manufacturers is the high degree of flexibility we employ to provide bespoke customer solutions.

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ONLY THE BEST FOR OUR CLIENTS. SAFELY THE BEST. IN SAFE HANDS WITH STOELZLE.
In May 2017, new regulations covering medical devices were formally published by the European Union—the EU Medical Device Regulation (MDR) and the In-Vitro Diagnostic Medical Device Regulation (IVDR). These new regulations must be implemented by medical device manufacturers by May 2020 and May 2022, respectively; however, as the new regulations address some of the ‘oversights’ of previous ones, some pharma companies may be unaware of the criteria now required of them, which could hypothetically lead to cases of non-compliance.

To discuss the intricacies and potential impacts of the new regulations in more detail, Pharmaceutical Technology Europe spoke with Volke Watzke, EU Medical Devices Sector manager, Domino Printing Sciences, and Elizma Parry, director, Global Clinical Practice at Maetrics.

Key aspects of the regulations

**PTE:** Could you briefly run through some of the main aspects of EU MDR and IVDR?

**Watzke (Domino Printing Sciences):** The key aspect of the EU MDR and IVDR requirements is focused on patient safety. The regulations will improve patient safety by requiring manufacturers to register every medical device (MD) and in-vitro diagnostic medical device (IVD MD) in the European database, EUDAMED. Each device will also be categorized in different risk classes depending on its risk to the patient. Class III is identified as critical risk, Class IIa/b is medium-to-high risk, and Class I is low risk. EUDAMED will link different platforms together and will cover registration information, certificates, vigilance, market surveillance, clinical investigation, and unique device identification (UDI).

The deadlines for the implementation of the EU MDR begin in May 2020. By this time every medical device sold in Europe will need to be registered in EUDAMED. EUDAMED has been postponed by two years due to technical difficulties linking the databases together but this postponement does not impact the legislative requirement to register each product UDI. The next deadline is the coding of Class III medical devices in May 2021. The deadline for coding on the packaging of Class II medical devices follows and then direct parts marking (DPM) if required of Class III medical devices. By May 2025, coding on the packaging of Class I medical devices will be required and DPM marking if required of Class II medical devices. Lastly, in May 2027, coding DPM if required of Class III medical devices.

With regards to IVD, the categorization of IVD MD is also divided into different risk classes. Class D is critical risk, Class C high risk, Class B medium risk, and Class A low risk. The initial deadline for complying with the regulation is May 2022 for registering every IVD MD in the database. The database will include information on the use of the device, the dimensions, the brand name, the product name, and the manufacturing company. A unique device–device identifier (UD–DI) will be required, which includes the Global Trade Item Number, as well as a unique device–production identifier (UD–PI), which includes an expiry date, batch number, and, if required, a serial number.

**Parry (Maetrics):** Drug–device combination products are either regulated as devices or medicinal products, depending on which component has the main intended use. When the drug element is the main intended use of the product, pharmaceutical companies are responsible for ensuring regulatory compliance. However, in the past, their main focus was the medicinal part of the product. In fact, in some cases, pharmaceutical manufacturers may have been unaware that they were affected by the Medical Device Directive (MDD). For instance, where the device component is considered as packaging, the need to ensure compliance may not have been apparent to pharmaceutical companies unfamiliar with device regulation.

This oversight in relation to device components has now been addressed with the arrival of the EU MDR; a lack of awareness of these new requirements could result in combination products...
being withdrawn from the market, as pharmaceutical manufacturers are now responsible for ensuring compliance of both the medicinal and device components of their combination products. A three-year transition period for the regulation began in May 2017, allowing manufacturers until May 2020 to review and implement the changes.

Industry impact

**PTE:** How will these new regulatory requirements impact the industry?  

**Parry (Maetrics):** For drug–device combination products, the key reference point of the EU MDR is Article 117. Article 117 is an amendment to Annex I of the Medicinal Product Directive and specifies that pharmaceutical companies must provide proof of conformity for the device part of combination products (if available) within the marketing authorization dossier.

What does proof of conformity consist of? There are three options. The first is to provide the results of a conformity assessment of the device part, showing compliance with the relevant general safety and performance requirements of Annex I of the EU MDR. This conformity assessment should be supported with the manufacturer’s European Commission declaration of conformity. The second option is to provide a certificate issued by a notified body, which allows the manufacturer to affix a European Conformity (CE) mark to the medical device. If there is no conformity assessment, and the involvement of a Notified Body is required, there is a third option. The applicant must be able to provide an opinion issued by a Notified Body, which shows that the device component complies with Annex I of the EU MDR. However, the Notified Body must be designated under the EU MDR for the type of device in question.

For its part, the EU IVDR affects companion diagnostics, which were not specifically mentioned in the preceding directive. The term ‘companion diagnostic’ refers to devices that help to determine patients who are most likely to benefit from a medicinal product, or patients who may be at risk of serious adverse reactions if they are treated with a certain medicinal product. Manufacturers have until 26 May 2022 to comply, but it is important for them to start the compliance process as soon as possible as they are reliant on two separate organizations, with different timelines for review: a notified body for the medical device component and a national competent authority for the associated medicinal product (or the European Medicines Agency). Companion diagnostics are categorized as Class C devices (Class D devices present the highest risk), so pharmaceutical companies must expect closer regulatory scrutiny from Notified Bodies and more stringent requirements.

**Watzke (Domino Printing Sciences):** For medical device manufacturers, the regulations will make a big impact. There is a lot of work to be done to ensure every product is registered in the EUDAMED database, a database that didn’t exist before. From what we understand, there are at least two million products in the market, and so complying with these new regulations is a big task. Some medical device manufacturers have very limited employees but sell up to 6000 products in a range of different product groups. The concept of basic UDI for registering each product group will be very helpful once implemented.

There are examples of medical device companies where around a third of the employees are working on fulfilling the requirements of the EU MDR. The regulation also has a large impact on the developers, due to notified bodies having to be notified by the EU authorities if new companies are founded or new products developed. Due to the complexity of the regulation, only five of the 57 former existing notified bodies for MDD and AIMDD have been notified and around an additional 40 have applied to be notified. Nevertheless, the regulation will be a step forward in terms of patient safety, as only registered products will be allowed to be sold in Europe and all databases will be linked.

**Stricter criteria**

**PTE:** How will the new regulatory submission information requirements for companies differ from those required under the previous regulation(s)?

**Parry (Maetrics):** The criteria for clinical data are stricter under the EU MDR, so it is critical that manufacturers get up to speed with what is needed. They must submit clinical evaluation reports (CER) that demonstrate clinical safety, performance, and clinical benefit. CERs must provide objective evidence to meet the specific related general safety and performance requirements in Annex I of the EU MDR.

As historical market clearance does not apply, every medical device must receive new CE marking under the EU MDR (no ‘Grandfathering’ allowed). It may be necessary to perform additional clinical investigations to obtain the necessary data. Manufacturers cannot rely on data from equivalent devices as they may have been able to do previously, unless they have contracted agreed direct access to the original data supporting clinical safety, performance, and clinical benefit of the medical device component. They must factor in enough time to perform clinical investigations to obtain the results, as well as relevant scientific literature. Notified bodies can also be expected to look for evidence of post-market surveillance, assessing how the device holds up once placed on the market and whether any complications occur in relationship to the device component. Ideally, standardized processes should be put into place so that this type of data is readily available and up to date.

**Delays not advisable**

**PTE:** How should companies proceed if they already have a CE marked drug-device combination product? Any advice concerning the extension deadline?
Watzke (Domino Printing Sciences): Every manufacturer producing combination products should be focusing on the normal deadlines, only in cases of uncertainty, should they resort to using the extension deadline. To ensure manufacturers are future proofing and to be seen as innovative, they should be meeting the deadlines outlined by the regulation. If they fail to do this, they ultimately may not be able to sell their product and they may not be a first-choice supplier for hospitals.

Parry (Maetrics): There is no grandfathering under the EU MDR, so all devices must have a new CE mark under the new regulation. Drug–device combination product manufacturers have until 26 May 2020 to make the transition and procure new CE marking. Products that currently hold a certificate under the current MDD 93/42/EEC can benefit from a variable extension period until their certificate expiry date, but this can be no later than 26 May 2024. However, it is important to note that no changes can be made to products during this extension unless they are re-certified under the EU MDR. Achieving compliance can be complex, so delaying the process of understanding and meeting the requirements is not advisable, especially taking into account factors such as the availability of resources and expertise, as well as the stretched capacity of Notified Bodies as a result of the new regulations.

Best practices
PTE: Are there any best practices you could share with pharma companies in terms of complying with these new regulations?

Parry (Maetrics): If they haven’t already, they should engage with Notified Bodies, where needed, right away to determine which organizations are designated or awaiting designation for the type of devices they will need to subject to conformity assessment under the EU MDR. It is important to secure a place in the queue, as so far, only nine Notified Bodies have been designated under MDR and only three under IVDR, and these will be under severe pressure for some time to come. Secondly, it is essential for pharma companies to familiarize themselves with medical device regulation, as they will be in new territory. It is essential to build up internal expertise or procure external support to make the process of understanding requirements and achieving compliance as efficient as possible. As the medical device industry moves towards greater harmonization and tighter scrutiny, the value of investing the necessary resources in compliance now cannot be stressed enough.

Watzke (Domino Printing Sciences): With the deadline for ensuring compliance with the EU MDR fast approaching, the time to act is now. Apart from the regulatory implementation and preparing the documents to share with EUDAMED and the notified bodies, coding of product packaging or on the product itself should be considered during the first steps of the overall project planning. The coding required to comply with the regulation could end up having a huge impact on the packaging design, the substrate that is used for packaging, and the size of the product. Therefore, it is important to consider at the beginning how the newly required coding will fit into the production process.

Reference
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