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While innovation and invention can sometimes be daunting, the willingness and capacity to harness automation and artificial intelligence to improve drug manufacturing is becoming a differentiator in the industry. Those who embrace, integrate, and perfect these new approaches stand to make significant gains over all rivals. Costs associated with a product recall in terms of human suffering, lowering brand status, and direct financial loss make new solutions highly attractive additions.

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On balance, effective adoption boils down to execution. Those who do not embrace methods, such as continuous manufacturing or intelligent process controls, will eventually lose customers and contracts while the industry moves forward. The real question becomes not should we, but when should we adopt, how, and which elements best suit our own niche. Rather than embarking on an ad hoc scramble to “keep up”, it appears wisest to continually track emerging trends that are going to require absorption. Journals such as Pharmaceutical Technology, Pharmaceutical Technology Europe, and BioPharm International are uniquely placed to carry some of this radar burden for you.

This entire set of decisions places an emphasis on direct experience and know how. Initially this rests on existing staff, or maybe those in combination with outside consultants who specialize in systems integration and legacy updates. However deployed, the way forward requires keeping an eye on innovation and invention as a key constant in a changing landscape. We are proud to continue being your partners in this endeavor.
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EDITORIAL

New Beginnings

Change of roster does not change the goal line. We are all patients first.

I have the privilege to step into the shoes of an industry powerhouse. For a decade, Rita Peters kept a steady and assured gaze on the pharmaceutical industry. She informed, she educated, but above all Rita maintained a faithful register of its many successes and milestones. My career began by setting the science agenda for biotech conferences. People were friendly. The air was brimming with optimism and adventure. Genetics rapidly became genomics, and human health was poised for transformation. I enjoyed the distinction of co-founding the Human Proteome Organization alongside my friend and mentor Ian Humphrey-Smith.

While gains have taken time, one can draw a straight line from those turn-of-the-millennia days to a growing body of successful cell and protein therapies. In the background, the bulk of the heavy lifting was achieved through the hard work of small molecules. As I write, three (non-intravenous) antiviral pills undergo clinical trials for COVID-19. Molnupiravir comes from Merck & Co. and Ridgeback Biotherapeutics. Another comes from Pfizer, known as PF-07321332, and AT-527, from Roche and Atea Pharmaceuticals. I mention these because they represent a sea-change from how we typically treat emerging pathogens. We have evolved and adapted to this new threat. The pharmaceutical industry has come a very long way from medicinal plants shipped in barrels.

Media outlets such as Pharmaceutical Technology, Pharmaceutical Technology Europe, and BioPharm International are not mere impartial observers. They help align the warp and weft of the development and manufacturing agenda. As we emerge from the shadow of COVID-19, the air brims with optimism and adventure again. We look forward to sharing our stories and learning from our readers. Our chief objective is to continue the legacy of excellence that is now synonymous with these publications so that we may learn from our readers. Our chief objective is to continue the legacy of excellence that is now synonymous with these publications so that we may build carefully upon the community and network our editors have long been integral to. It is my honor to work alongside a strong publishing team including expert editors Jennifer Markarian, Feliza Mirasol, Meg Rivers, Felicity Thomas, Susan Haigney, Grant Playter and publisher Mike Tracey. The team roster has changed, but not the goal line. PT

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In an important step for modernizing drug formulation and biopharmaceutical development, FDA is launching a program to test the safety and suitability of novel excipients for use in new drugs and biologics. This final initiative, first proposed two years ago, will support a pilot program to test up to four novel excipients likely to improve the effectiveness and safety of important new drugs (1). The aim is to encourage sponsors of clinical trials to test new drugs formulated with excipients that FDA finds acceptable for use under this program.

FDA announced the pilot program Sept. 7, 2021, and spelled out the application process in a Federal Register notice (2). The notice explains that the pilot is open to novel excipients that have not been used previously in food or in FDA-approved products. Excipient manufacturers seeking to participate in the pilot should submit information on the novel inactive ingredient and its potential for enhancing health by offering pharmacokinetic characteristics important to developing new drugs, as described in an outline for an initial proposal (3). The sponsor also must show it can produce a complete information package in the set time frame for weighing pilot proposals. Initial pilot review proposals are due at FDA by Dec. 7, 2021.

FDA defines a novel excipient as an inactive ingredient that is not fully supported by existing safety data related to a proposed level of exposure, duration of exposure, or route of administration. Manufacturers should describe how the product addresses a public health need and advances drug development, such as by increasing solubility for an oral formulation taken chronically. Sponsors also should describe available quality and toxicology information that support the product’s safety, such as pharmacokinetic/toxicokinetic data and other nonclinical information, as presented in FDA guidance issued in 2005 (4).

From these submissions, FDA will select four products for full review under the pilot, planning for two during the first year. Selected participants then should provide a full data package of toxicology and chemistry, manufacturing, and controls (CMC) quality data, as required for excipients. If the excipient passes muster, FDA will determine that it may be used in the formulation for an experimental drug undergoing clinical trials, provided that the sponsor demonstrates that it is safe to use in that therapy. After FDA approves a new drug or biologic utilizing the new excipient, that excipient would then be added to FDA’s Inactive Ingredient Database, making it available for use by other manufacturers, including those producing generic drugs.

Manufacturers of drugs and biologics, as well as excipient developers, have long sought a process for FDA to evaluate new inactive ingredients prior to use in a new drug or biologic. Manufacturers of drugs and biologics, as well as excipient developers, have long sought a process for FDA to evaluate new inactive ingredients prior to use in a new drug or biologic. A perennial difficulty is that new drug sponsors are reluctant to delay or complicate FDA review and approval of an investigational new drug (IND) for an experimental therapy due to the need to assess an untried inactive ingredient in the product formulation. Yet, these firms increasingly face difficulties in formulating innovative products with available, established excipients. Bio-

Jill Wechsler

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pharma companies have expressed support for the pilot as a way to address these development challenges, such as the need for new ways to stabilize proteins for bioavailability in new formulations. Excipient makers similarly acknowledge that they would be more willing to invest in production, controls, and characterization of novel excipients if it’s possible to gain FDA review of the product’s benefits outside of clinical testing for a new molecular entity.

FDA first proposed this process for evaluating novel excipients separate from new drug applications in a Federal Register notice posted in December 2019 (5). That draft plan asked manufacturers to comment on the proposed program, its definitions and scope, and FDA sought to address these issues in this final proposal.

It appears fitting that FDA is launching this novel excipients pilot program as the International Pharmaceutical Excipients Council, IPEC-Americas, marks its 30th anniversary. IPEC held its first meeting in March 1991, with the aim of harmonizing excipient standards set by different pharmacopeias and to address worldwide issues important to excipient use. Manufacturers of these essential ingredients in pharmaceutical formulations note that many well-known excipients that have been used for decades are not suited to the novel dosage forms and parenterals under development today (6). Industry also would like to see an update of FDA’s 2005 guidance on excipient safety testing, mentioned previously. These initiatives, as well as ongoing efforts to set international standards for excipient use, have potential to enhance drug formulation and support modern manufacturing and quality control efforts.

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Automating Aseptic Manufacturing

Jennifer Markarian

Conventional and robotic automation inside closed systems reduces risk.

An ongoing engineering challenge for aseptic drug manufacturing is to reduce the risk of contamination as much as possible. As it is well known that human operators are the biggest source of contamination in a cleanroom, a growing consensus is that automated systems that eliminate human intervention are the future of aseptic processing. Pharmaceutical industry experts point to the successful use of both conventional and robotic automation in other industries, such as semiconductor manufacturing and aseptic food processing, as well as in pharmaceutical packaging and warehousing, as a sign that the pharma industry should overcome its reluctance to change. This shift has begun in fill/finish processes and is moving further upstream into other aseptic manufacturing steps. Robotic technology, in particular, is finding use in drug compounding (1) and in closed, gloveless isolators.

Advances in robotics

While conventional automation is suited for larger volume operations with simple motion and few changes, robotic automation technology designed for cleanrooms offers the ability to perform different types of operations and handle multiple formats, such as vials and syringes. Robots, which can perform the repetitive tasks otherwise handled by human operators, enable the move to closed systems that can operate without human intervention.

“Over the past 30 years, the equipment evolution has been from open and manual, [to] isolated and manual, then isolated and automated, and [now] closed and automated. In the next 5–10 years, more robotic solutions will come into the pharma production world throughout all segments, driven by new regulations, more personalized medicine, and more flexible machines,” predicts Rudolf Michael Weiss, global head of pharma robotics at Stäubli Robotics.

Regulatory authorities have expressed support for automation technologies as a means to limit aseptic interventions, notes Laura Moody, North American product manager at machine builder Syntegon Pharma Technology, pointing to as far back as FDA’s 2004 aseptic processing guidance (2) and to recent conferences. “Even as recently as the 2021 International Society for Pharmaceutical Engineering Aseptic Conference, the reduction in risk to the drug product through the use of automation and robotics was reiterated by FDA representatives,” says Moody. She says that acceptance by regulatory authorities and pharmaceutical manufacturers is helping drive innovations in robotics.

Operating multiple-product filling lines in accordance with the European Union’s draft Annex 1 (3) can be achieved with various technologies. One method is to use restricted access barrier systems (RABS) with fully automated, hydrogen peroxide decontamination of the entire cleanroom prior to each batch, says Arno Schroff, director of site and plant development at contract development and manufacturing organization, Vetter. Closed iso-
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lators are another increasingly important solution. “Our long-term vision is shifting from a human-centered production towards a fully automatic process with robotic equipment to further reduce possible risk to the product,” he notes.

“The biggest news from the past year is that FDA and Health Canada have approved commercial products made using gloveless robotic isolators. Several of our customers have achieved this milestone,” says John Harmer, head of sales and marketing, aseptic filling, at Cyntegon, which acquired Vanrx, a manufacturer of robotic aseptic filling machines, in February 2021. “The industry has moved beyond ‘Will they work?’ to ‘Where else can we use them?’ Our prediction is that robotics will play an increasing role in manufacturing personalized medicines including mRNA, peptides, bacteriophages, CRISPR-Cas9, and other genomic therapies.”

Reducing contamination

Compared to conventional RABS or isolator-based filling systems, gloveless robotic isolators eliminate human intervention. “The sources of interventions have to be designed out and built around the capabilities of robotics,” says Harmer. “Because these systems are standardized, they can cut a year off the typical process of building filling capacity. Robotics handle vials, syringes, and cartridges the same way within presterilized tubs, so flexibility is built in for the small-volume, high-value drugs that currently fill biopharmaceutical pipelines.”

Syntegon’s new robotic fill/finish system, the Versynta FFP [Flexible Filling Platform], was introduced in mid-2021 and is designed for small batches of up to 3600 containers (vials, syringes, or cartridges) per hour. The company’s microBatch system, currently in development with Vetter, is an automated production cell with a gloveless isolator designed for even smaller batches of 120–500 containers per hour, says Moody. She notes that this system is currently in the detailed design phase and is expected to be launched in 2022.

Both solutions use robotics; while Versynta FFP uses a four-axis robot, developed by Syntegon, to transfer containers from one station to the next without glass-to-glass contact, Versynta microBatch is a fully automated production cell. It is designed for flexibility in the types of containers and closures that can be processed. “It allows for the container and closure of a drug product to be dictated by the needs of the drug and usage of the patient, not the limitations of the fill/finish machine,” comments Moody.

The gloveless isolator also eliminates the need for glove testing and glove management; features integrating air management, so that the isolator does not need a technical ceiling or interfaces to the building; and the design is standardized to allow quick delivery and validation, notes Moody.

Schroff adds that an automated de-bagging system for presterilized packaging components eliminates human intervention to prevent contamination of materials entering the isolator. Automated line set-up, monitoring, and fill-weight checks for process control are other benefits, he notes.

The flexibility and rapid changeover required for fill/finish of small-batch parenteral drug products is better met by robotics than by traditional automation, agrees Joe Hoff, CEO of robotics manufacturer AST. Efficient cleaning, reliable sterilization, and high overall equipment effectiveness are other drivers for growth in demand of these systems, he adds. “The biggest challenges engineers face when designing isolated fill lines are fitting the design into a small, enclosed space; achieving good operator ergonomics; and ensuring all systems and penetrations are leak-tight and properly designed for cleanliness and [hydrogen peroxide] sterilization,” says Hoff.

Although some may still hold the misconception that robotics can’t be used in cleanrooms because moving parts may generate non-viable particulates, this concern has already been resolved, suppliers say. Robotic suppliers point out that robots for pharmaceutical cleanrooms have a hygienic design for low particulate generation and resistance to standard cleaning chemicals. They can also be designed to be resistant to hydrogen peroxide so they can withstand frequent decontamination.

Another aspect of design is planning for changing parts and performing maintenance. Xavier Gómez Garcia, lyophilization portfolio manager at pharma equipment and engineering supplier Telstar, points out that haptic interfaces allow users to remotely manipulate a robot. “Some of these devices allow the user to also feel the weight of the real object, even without physically touching it. The precision is extremely high. [Systems could have a] built-in feature to change format parts and do basic maintenance through telematics [remotely operated] haptic devices, without the need of glove ports or operators near the process zone,” suggests Garcia.

Software for improving robotic motion continues to be improved. “The robot is embedded into the [information technology (IT)] structure of the machine, and new software features like tele-manipulation, remote joystick fault intervention, and [motion controls such as] anti-sloshing movements, for example, need to be developed,” says Weiss. He notes that Stäubli is currently developing specific pharma software features suited to robotics inside isolators.

Increasing predictability

In addition to lowering the risk of contamination, robots increase predictability. Compared to robots, humans can have difficulty being consistent with repetitive tasks requiring precision and accuracy, suggests Toni Manzano, co-founder and CSO of Aizon, a pharma/biopharma software as a service provider and co-chair of the Parenteral Drug Association’s first Robotics and Automation conference held in April 2021.

While people need to be trained and periodically retrained—and it can be challenging to duplicate a process in multiple locations—robots are trained once and have the same precision no matter what the time, day, or location, adds Martin Dublin, managing director of consultancy One One Eleven GmbH and co-chair of the PDA conference with Manzano. High levels of standardization across multiple facilities simplifies operation and inspection.

Another benefit of robotics is easier qualification, says Alex Armengol, international senior sales director for SP
ARMENGOL. AI can identify process deviation, such as supervisory control and data acquisition systems. In addition to machine data, data from process analytical technology (PAT) tools, used in automated systems, can improve quality and efficiency. In-process control (IPC) check-weighing in an automated filling system is one example, notes Armengol. Conventionally, check-weighing was a destructive test, but using the PAT tool of IPC, each container is weighed and no product is lost. "In this method, [empty] containers are placed on an in-process balance or load system, and the exact amount of product is dispensed and checked against the specification. Over a period of time, if the controller senses any changes to the fill weight, the system will adjust the pump appropriately," he explains. Additionally, artificial intelligence (AI) algorithms can use data to predict machine behavior and potential failure points, adds Armengol. AI can identify process deviations, and decisions can be made in real time to reject or accept products.

These data can also be used by process experts. For example, Harmer says, "If the filling system contributes to a consistent stream of data about a customer’s manufacturing process, we have better evidence to optimize processes or improve drug product quality."

Today’s machines are highly integrated into IT systems for sharing data such as batch records or for allowing remote viewing of machine performance or remote maintenance, but machines in the future will advance into intelligent feedback and even predictive maintenance, suggests Hoff.

Using AI in “smart” systems, set up to make decisions based on input from the process and algorithms derived from process knowledge, will increasingly play a role in automation systems.

“Smart systems, understood as the interaction between machines and AI, are able to repeat tasks consistently and, if they are well trained, make the right decisions in a systematic way,” explains Manzano.

A concern about how regulatory authorities will accept critical decisions being made by automated systems rather than human operators is creating hesitancy in pharma manufacturing. Other regulated industries, as diverse as banking and food manufacturing, have adopted fully automated mechanisms managed by AI, notes Manzano. One example of AI being adopted in pharma manufacturing is smart systems for feeding raw materials. He says that questions such as: “How do I proceed if a lot of raw material is finished in the middle of the mixing operation? Can I add a lot of the same substance from another supplier?” are examples of unusual situations that can be properly managed by AI connected to an automated system.

Handling of these types of questions would need to be validated, adds Dublin, who notes that a lack of experience by regulatory authorities is currently a limitation. Internal company inspectors also need to gain experience and confidence in smart systems.

Another area that has been tested and found to be successful is automated inspection of pharmaceutical finished products, managed by AI.

“AI has demonstrated a high value and a consistent response in complex tasks, including defect identification, deviation detection, multivariable control, and chained actions based on different scenarios, for example,” says Manzano. Good data that are digital and not managed in silos, but rather collected via the Internet of Things and managed via cloud technologies, are crucial for accurate AI results, he cautions.

“The way forward is to consider the whole process; digitalization yields the data needed to train robots or automated systems,” agrees Dublin.

Training

Control systems for robotics are complex systems, and training is crucial for operating and maintaining these systems. “Automation and control are key to successful implementation of robotics, including the understanding of the mechanics and electronics involved in making the robots function as intended,” says Armengol. “Key to the training is the interface between the machine and the operator, known as the human machine interface or graphical user interface.”

Armengol suggests that hands-on training is critical for these systems. SP i-Dositecno is currently installing a modular robotic filling line and isolation system at the National Institute for Bioprocessing Research and Training (NIBRT) in Dublin, Ireland, which will be used in NIBRT’s aseptic biopharmaceutical fill/finish training.

Harmer points out that for automated systems, operators do not need to be trained in aseptic techniques, as they do in conventional systems. Instead, training focuses on the workcell’s integration of robotics and the closed isolator. “In Cytiva’s training, users learn how the aseptic process automation works, how to create recipe-driven processes for specific drug products, and how the machine controls risk at each stage of the aseptic filling process,” he explains.

Barriers to automation

Despite the benefits of automation and the inevitable use of automation in facilities of the future, there are multiple
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barriers to upgrading existing facilities with new, automated lines, including the need to revalidate and the initial investment cost. Armengol notes that for small- and some medium-size companies, this cost barrier may be difficult to overcome.

Although industries such as semiconductors had a strong business case to automate because of their narrow profit margins, biopharma, with its higher profit margins, has less incentive to change, suggests Manzano. On the other hand, says Dublín, recalls and batch losses are costly, so a business case for automation can be made.

“Roadblocks to modernizing a fill/finish cleanroom are regulatory, cost, capacity, and time,” agrees Hoff. “Unless a facility has an unused or available fill suite they can expand into while maintaining their existing fill suite, it is unlikely they have the time or capacity to shut down a validated and qualified process to modernize.”

In addition, the design of existing facilities and equipment may not be conducive to automation. “Retrofitting within an existing machine is usually difficult due to the lack of space and freedom of movement for the robot,” notes Moody. One option is to automate the secondary processes, such as the supply of packaging materials, around the existing machine, she suggests.

Autonomous mobile robots and automatic guided vehicles for transporting materials are an example of automation that can be applied to existing processes, agrees Weiss.

Another challenge is the reluctance to replace humans with robots. The lockdown restrictions of the COVID-19 pandemic that created worker shortages have made the consistent availability of robots more appealing, but the concept of this change in work still creates hesitancy. Although it is true that implementing automation will eliminate certain types of jobs, it will create some others that need different skills, says Dublín. Not wanting to change operators’ jobs shouldn’t override the benefits brought by digitalization and automation. “It is the responsibility of enterprises to adapt,” he asserts.

Ongoing implementation ahead

Despite some barriers to use, the advantages of and continued improvement in robotic automation will drive continued implementation in aseptic processing, experts agree.

“To date, the strength of robots is primarily in performing repetitive tasks, and [robots] have so far been less suitable for constantly changing ones. But a lot is happening in this area right now,” says Moody. “The limits will continue to shift due to new technologies such as AI and reduced costs for robotic solutions. Going forward, we will be able to equip all areas needed for the operation of a filling machine with robotics. Examples of future robot applications include upgrading the filling path or inserting and changing sediment plates for microbiological monitoring.”

“Robots will become mainstream [in pharma manufacturing] within the next few years because of enhanced flexibility, repeatability, and precision,” adds Armengol.

Garcia suggests that the pending publication of Annex I is driving demand for plant retrofits. “New regulations are clearly accelerating the change in the pharmaceutical industry, encouraging both drug companies and equipment manufacturers to embrace new technologies that can minimize the risk of contamination for the final product. Annex I is pushing the industry towards automatization, [particularly] in critical processing zones, including all the operations in primary packaging, filling, and capping, [which generally have] freeze dryers in between,” says Garcia. He notes that new, automated loading and unloading modules for freeze dryers and autonomous filling and capping stations that incorporate PAT tools are being used.

“In the past 25 years, primary packaging lines have evolved from dozens of manual operations, typically through glove ports, to fully automated lines. Until now, automation has been quite rigid to fulfill high production volumes in centralized manufacturing plants,” notes Garcia. The growing need for sterile manufacturing of smaller batches, however, is driving growth of more flexible robotic automation. “In my opinion, companies with centralized factories will work together with new and flexible plants where [good manufacturing practices] robots will play a crucial role. Local manufacturing hubs with an agile supply chain will be a vital asset,” he predicts.

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Drug makers go beyond continuous improvement and green chemistry to increase the sustainability of API manufacturing.

In the latest Intergovernmental Panel on Climate Change report issued in August 2021, the organization stressed that while some impacts of climate change cannot be reversed, such as continued sea level rise, “strong and sustained reductions in emissions of carbon dioxide (CO₂) and other greenhouse gases (GHGs) would limit climate change” going forward (1).

The pharmaceutical industry, like other manufacturing sectors, contributes to CO₂ and GHG emissions and is aware of the need to increase the sustainability of its operations. The IQ Consortium’s Green Chemistry Working Group first met with FDA in 2012 to identify opportunities for promoting green chemistry (2).

The IQ Green Chemistry Working Group also adopted the Green Aspirational Level (GAL)—originally developed by Boehringer Ingelheim (3,4)—as a standardized green efficiency goal for API manufacturing processes that factors in the complexity of the synthetic route; the consortium also developed a Green Scorecard to show the value-added impact of green chemistry and other improvements, including process simplification (5). Individual manufacturers are tackling the issue in many different ways.

**Beyond continuous improvement**

Small-molecule API manufacturing, according to Scott Martin, general manager of W. R. Grace & Co.’s Fine Chemical Manufacturing Services (FCMS), is driven by continuous improvement. “Most companies have pursued continuous improvement programs for many years, and many like Grace FCMS have embedded sustainability into those programs,” he says. “The expectation of sustainable manufacturing and the sustainable use of resources is top of mind for everyone in the industry,” he adds.

More specifically, Martin notes that both increasing yields and increasing throughput by definition result in a reduced environmental footprint. In addition to these types of efforts, improvements are also being made with respect to sources of energy, with drug manufacturers pushing utilities to produce more renewable energy, he continues. “As we see it, being more sustainable and pursuing continuous improvement are not two separate issues,” he concludes.

Many technologies for ensuring cleaner energy consumption, abating emissions, and improving waste management have already been developed and, thus, are easier to implement and have more acceptable payback periods, adds Brian Peutherer, health, safety, and environment director at Sterling Pharma Solutions. “For contract development and manufacturing organizations (CDMOs), these solutions are the easiest way to make a significant impact on the sustainability of products without actually impacting API design,” he notes.

Sterling, for instance, has invested in a bio plant to treat wastewater, an anaerobic digestion plant to generate energy from waste, and a combined heat and power plant that generates approximately 98% of the energy used at its headquarters in Northumberland, United Kingdom.

**Green chemistry and beyond**

The concepts of green chemistry and sustainability, according to Jeff Song, vice president of chemical development in the United States for Boehringer Ingelheim (BI) Pharmaceuticals, have been broadly accepted in the pharma industry for the past 15 years. At BI, he says, these concepts are incorporated into daily work, leading to the routine development of greener API processes for all projects through innovative chemical research as well as new technologies.

To achieve true sustainability, though, Song emphasizes that other approaches than green chemistry principles should be considered, such as developing an effective waste management protocol at the end of the process. “Some modifica-
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tions should be also made to the supply chain by replacing existing methods with greener commodity chemicals and materials and by reducing chemical steps to convert commodity chemicals into value-added building blocks for API synthesis. While efforts have already begun within the industry to track the greenness of chemical processes at building-block suppliers, more work is needed," he observes.

BI, adds Frederic Buono, the company’s senior associate director of chemical development in the US, looks to design the most direct synthetic approach with the least number of chemical steps using commodity chemicals as early as possible in the API development cycle. The commodity chemicals should have minimal cost, short methods of preparation, and wide availability. There is also a focus on process optimization to reduce waste generation and energy consumption by minimizing reaction concentration and avoiding extreme reactions condition (e.g., cryogenic temperatures).

As a member of the American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable, BI researchers have also helped to develop tools to measure process performance with respect to sustainability and greenness, including the innovation Green Aspiration Level (iGAL) (6).

Looking to synthetic biology
The petrochemical industry is vital to the pharmaceutical industry today as a supplier of key raw materials used for the production of most synthetic-chemistry-based pharmaceuticals. It also, however, accounts for a large percentage of the world’s energy consumption. According to Jing-Ke Weng, cofounder of Double Rainbow Biosciences, a professor of biology at the Massachusetts Institute of Technology, and a member of the Whitehead Institute, current small-molecule intermediate/API manufacturing almost entirely relies on unsustainable precursors.

“The growing need to quickly move away from fossil fuel amid the threat of climate change creates urgent demand for novel sustainable approaches to replace the current supply chain for small-molecule drug production. Other than sporadic uses of biocatalysts in specific steps of some pharmaceutical syntheses, truly sustainably produced synthetic small-molecule pharmaceuticals are very rare,” Weng asserts.

The pharmaceutical industry, like other manufacturing sectors, contributes to CO₂ and GHG emissions and is aware of the need to increase the sustainability of its operations.

Synthetic biology that integrates metabolic engineering of various biological hosts (e.g., bacteria, fungi, and plant cells) and enzyme engineering, Weng believes, will be a major solution that will lead to the next green revolution in the way future small-molecule pharmaceuticals will be produced. “Several proof-of-principle studies have shown the feasibility of employing biochemistry instead of synthetic chemistry to produce complex drug-like molecules sustainably; however, we are still far from widely adopting this new approach as a new industry standard,” he comments.

The first step, Weng predicts, will be the gradual replacement of synthetic chemistry production processes for small-molecule intermediates/APIs with enzyme-catalyzed reactions, which he notes are usually efficient, highly selective, and occur under mild conditions.

Begin at the beginning
To contribute to the reduction of CO₂ and GHG emissions, all drug developers and manufacturers need to seriously consider measures to improve sustainability throughout each phase of their industrial processes, according to Weng. “The pharmaceutical industry is due for a major overhaul in all aspects of its unit operations. Essentially, the pharmaceutical industry should be evaluating sustainable alternatives for all current exercises that rely on fossil fuel inputs,” he sates.

“The optimal time to consider sustainability is before the construction of a manufacturing plant, and at the design phase of the synthetic route, as these are the stages at which the most efficient technologies and techniques can be incorporated,” Peutherer asserts. “Considering sustainability from the outset allows the opportunity to integrate sustainability into every stage of a molecule’s lifecycle,” he continues.

Buono agrees that sustainability should be considered throughout the API R&D process starting from medicinal chemistry all the way to commercialization, but with different emphasis for each. “In our opinion, one should strive to implement new synthetic routes (hence those with a much higher level of sustainability) starting with the first clinical batch or shortly thereafter to achieve a balance between the overall speed, sustainability, and attrition rate.”

From the point of view of CDMOs, the greater focus on sustainability in the pharmaceutical industry requires greater collaboration with customers at an earlier stage of project planning and development to incorporate sustainable manufacturing techniques into the API process design, according to Peutherer. "Relationships with supply chains are critical when considering the impact of manufacturing on the environment to ensure expectations are clear, and standards are maintained throughout the supply chain process. This safeguards against companies passing on their environmental burden to others,” he says.

The best time to consider optimal, sustainable production solutions is during the design of the synthetic route to an intermediate/API, notes Martin, because once these processes are validated, it is very challenging to introduce any changes, even if they
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offer significant improvements in productivity and sustainability.

In addition to identifying transformations that require minimal energy inputs, Martin also remarks that it is beneficial to choose solvents and other reagents that if not consumed in the process can be recycled or at least reused or repurposed in some way.

Companies should become more comfortable with using non-virgin, reclaimed solvents, Peutherer agrees. “Solvents often make up the bulk of materials used in API manufacturing and reducing their use can play a huge part in lowering a process’s costs, carbon footprint, and waste management requirements,” he observes. It is also important to consider other alternative raw materials used in production that have a lower environmental impact.

**Intensify operations**

There are many opportunities to improve operations no matter what type of chemistry or chemical products are involved, according to Martin. He points to crystallization as one area that could use some attention. “Many small-molecule intermediates and APIs are solids and automatically purified via crystallization, which requires the use of solvents and often low temperatures. Under certain circumstances, distillation can be a more effective approach,” he explains.

There are, in fact, many opportunities to increase process greenness and sustainability by intensifying unit operations, Buono observes. For example, solvent volumes can be limited using a continuous extraction process, and aqueous/organic separation during work-up can be maximized using some separative commercial membrane units.

**Keep things flowing**

Flow chemistry is one of the technologies being employed to some extent in API manufacturing to increase sustainability, because, according to Song, the principles of green chemistry and green engineering are both leveraged in this manufacturing approach.

The versatility of the batch reactor has, until recently, meant any gains from continuous processing were previously unjustifiable, notes Peutherer. “With improving technology and techniques, however,” he notes, “continuous processing, especially in tandem with process intensification, can majorly impact on the inherent safety of a process and lower utility demands, as well as improving process specificity and reducing waste.”

Continuous flow technology, says Buono, can enhance heat and mass transfer by shortening process times with precise residence time control, which can lead to increased safety and reproducibility and thus afford product quality, all combined with easy scalability. “For these reasons, flow chemistry may offer a more sustainable technology for chemical synthesis compared to traditional batch chemistry,” he says.

In one example, BI developed a convergent, robust, and concise synthetic route which reduced the overall complexity (by eliminating a deprotection step) for an API that leverages a continuous flow-based Curtius rearrangement (the thermal decomposition of an acyl azide to an isocyanate with loss of nitrogen gas) (7). The overall process is 160% greener than the industrial average and 58% more efficient than the original batch process, according to Buono.

It is important to remember, though, notes Martin, that flow chemistry, while useful in some cases, is not applicable to all. Drugs produced in only small volumes, such as orphan cancer drugs, will likely not benefit from a continuous process because only limited quantities are required. In addition to lengthening development timelines for drugs where speed to market is essential, the upfront investment in the design of processes and equipment may not be easily recovered.

**Role for digital technology**

Digital technologies will play a crucial role in enabling greater sustainability of small-molecule API development and manufacturing. “We need to embrace digital technology to revolutionize the drug discovery process, and to adopt artificial intelligence and machine learning into our processes,” Song asserts. Doing so, he adds, is in concordance with Chemistry 4.0, which calls for the implementation of more digitalization and lab automation. “To achieve these goals, collaboration across the industry is crucial,” says Song. “Pulling together expertise and insights from chemists, process engineers, theoretical chemists, IT specialists, and computer scientists will allow us to efficiently develop the digitalization solutions of the future for application to process development,” he concludes.

**Regulatory cooperation needed**

Ideally improvement of the sustainability of all drug manufacturing processes should be achieved; however, the pharma industry needs to establish a mechanism for addressing the shortcomings of older, existing processes for previously approved drugs.

“Altering existing processes is always challenging, but the urgency of available climate projections suggests the effort will be well worth it in the long run,” asserts Weng. “The near-term investment in sustainable solutions will push the industry towards more efficient API production processes while leaving a greatly reduced carbon footprint,” he adds.
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In addition, Weng suggests that given the threat of global climate change, a failure to proactively embrace sustainable solutions may result in environmental regulatory agencies mandating sustainability targets for pharmaceutical manufacturers and other chemical industries.

Currently, it is extremely time-consuming and costly to implement changes due to the complex regulatory process that is involved. One possible solution, notes Martin, is to offer simpler regulatory pathways for certain types of changes related to sustainability improvements that do not affect the intermediate or API itself.

In cases where alterations to processes are a challenge, Peutherer says the best way to achieve a more sustainable outcome is through gains in ancillary aspects: cleaner energy generation, improved waste treatment options, pollution incident prevention, and carbon offsetting. This lowers the overall carbon footprint of the manufacturing.

Weng believes, though, that as sustainable means of small-molecule pharmaceutical development are expanded and tested to validate their performance against conventional synthetic chemistry-based approaches, industry peers and regulatory bodies must work together to embrace these solutions.

**Always moving forward**

All drug manufacturers are faced with these challenges. Contract manufacturers such as Grace FCMS work with customers to push the adoption of more sustainable solutions as part of continuous improvement efforts. “It is a combined effort that includes increasing yields, using more sustainable raw materials, and more environmentally friendly packaging equipment to recycling and reuse of solvents and shipping containers, all with the goal of reducing the environmental footprint of small-molecule intermediate and API manufacturing,” Martin states.

“Sustainability,” Martin continues, “is now at the forefront. Most public companies have sustainability targets and hold regular discussions with suppliers regarding their sustainability expectations. Grace FCMS is therefore continually looking at ways to help customers reach their sustainability goals while ensuring continued supply of high-quality API product on time and in full.”

New changes will continue to be made and observed due to the enhanced awareness and continued innovation, agrees Song. “The power of machine learning and digitalization will quickly bring the most efficient synthetic pathways to chemists, not only for reaction design but also for process optimization,” he notes.

**Flow chemistry is one of the technologies used in API manufacturing to increase sustainability.**

Improvements to be made across the industry can be implemented in two ways, according to Peutherer. “Firstly, gradual improvements in the processes that companies presently undertake or redesigning of operations (e.g., microwave versus traditional oven drying) will have cumulative impacts. Secondly, on a more process-specific level, implementation of environmental operation studies at the concept stage, and waste audits on longer-running processes, can bring tremendous benefits,” he explains.

In the near term, Peutherer expects the greatest gains to be made in areas not directly associated with processes, including utility consumption and waste prevention/treatment. “For example, at Sterling we treat waste on site and are currently building an ‘energy-from-waste’ plant as part of our strategy to reduce the company’s overall carbon footprint,” he comments. Longer term, Peutherer predicts wider application of the green chemistry principles and improvements in API design and manufacturing processes will have a major impact on the industry.

Progress that has been made to date should be recognized too, Song adds. He points to the growing development and adoption of flow chemistry for API synthesis, and recent advances in catalysis, particularly in biocatalysis and non-precious metal catalysis (copper, nickel and iron), that offer an improved ability to build complex molecules with much higher efficiencies but less waste. Interest is also resurging in the photochemistry and electrochemistry due to the inherently green nature of these technologies, especially when coupled with flow technology.

Double Rainbow, according to Weng, employs two unique sustainable technology platforms to produce sustainable therapeutics: rich glycosylation biochemistry in all domains of life to produce glycosylated drug products that harbor unique pharmacological activities but are too difficult to be made using conventional synthetic chemistry methods and bioengineered microbial systems to recreate valuable medicinal natural products that are traditionally sourced from fragile natural ecosystems.

“In the near term, we anticipate moving several of our promising early-stage sustainable therapeutic candidates to clinical trials. Longer-term, we believe our bioengineered therapeutics will emerge as a new class of therapeutic modalities that play important roles in the future of health care while contributing to the sustainability of our planet,” Weng concludes.

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Considering Bio/Pharma Reformulation Strategies

Felicity Thomas

Reformulation strategies are useful tools for more than just stretching out the potential return on investment for a product.

The evolution of drug development is well known to be inherently costly and associated with a significant risk of failure. It has been reported that, on average, companies can spend $2.7 billion in bringing a drug through the full product lifecycle (from invention to commercial launch) in a process that can last between 10 and 15 years with a 90% rate of failure (1).

As a result of the significant cost of development, companies seek to recoup finances through data exclusivity and patent protection of intellectual property, such as the drug product’s formulation. When the drug is nearing the end of its patent or no longer has market exclusivity, reformulation strategies can be a useful tool to stretch out a potential asset lifecycle.

However, reformulation strategies are not just a means of elongating market presence for drug products or maximizing the potential return on investment. Bio/pharma companies reformulate existing therapies for a whole host of reasons, such as treating underserved or neglected disease areas, improving patient adherence (particularly for target patient groups, such as pediatrics), reducing the potential of drug abuse, and providing alternative options in crisis situations—as has been apparent during the COVID-19 pandemic.

Treating new indications

Many existing therapies have undergone reformulation to provide treatment options for other disease areas. For example, minoxidil, which was originally formulated as a tablet to treat hypertension, has been reformulated for topical use to treat male pattern baldness (2). Additionally, drugs have been repurposed for new indications when they have failed clinical trials or were withdrawn for safety reasons. For example, sildenafil was originally formulated for the treatment of angina; however, the therapy did not successfully complete clinical trials for this purpose. Pfizer then invested in research around an observed erectogenic side effect, and it has since been reformulated for the treatment of pulmonary arterial hypertension (2).

Recently, researchers have been evaluating the potential of formulations of pentamidine with Pluronic (BASF) micelles, which act as drug solubilizers or controlled drug-release agents, to treat Human African trypanosomiasis (HAT or sleeping sickness)—a neglected tropical disease (3). Pentamidine is an anti-infective agent that can be used to treat an earlier stage of the disease; however, it is unable to penetrate the blood-brain barrier sufficiently to treat the secondary stage of HAT. Therefore, it was hypothesized that a combined pentamidine-Pluronic formulation may be a suitable approach to provide patients with a single therapeutic option for treatment of all stages of HAT. Although, due to time and money constraints, the researchers were unable to significantly enhance brain exposure of the active ingredient using a formulation incorporating Pluronics, they did produce a significant body of high-quality data for use by other researchers in the future (3).

In other research, a new formulation of risperidone is being investigated, repurposing the therapy from an antipsychotic to an adenocarcinoma treatment (4). Previous work has been inconclusive on the anti-cancer benefits of risperidone, although it has been used off-label in the palliative care of late-stage cancer patients. In the study, the researchers explored the formulation of risperidone with a naturally-occurring conjugated linoleic acid (rumenic acid) and lipid excipients—VAL401.

When compared with conventional risperidone therapy, the researchers found that the reformulated drug in a lipid excipient resulted in a similar rate of exposure to the active moiety. As a result, it was concluded that the phar-
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macokinetic data attained supports the use of safety and tolerability data from the conventional risperidone formulation for further testing of VAL401 (4). Based on these results, it is hoped that the drug will be able to proceed into later stage clinical trials with the original drug’s established profile being used to appease regulatory requirements.

**Improving patient adherence**

Patient adherence or non-adherence to a therapeutic regimen can mean the difference between success or failure in terms of treatment. Adherence to a medication regimen can be particularly poor for elderly patients, pediatric patients, and patients dealing with chronic, long-term diseases and disorders.

Alterations to the route of administration can be a useful tactic to help improve patient adherence. Moving away from intravenous injections to subcutaneous ones, for example, can lower both the burden on the patient and healthcare providers, as care can be provided in a home setting. Or, utilizing a delivery technology, such as orally disintegrating tablets (ODTs), could facilitate administration of oral dosage forms to pediatrics and patients who struggle to swallow tablets.

For the latter example, a recent deal between Catalent and Edenbridge Pharmaceuticals was agreed upon for the formulation of glycopyrrolate as an ODT form (5). Glycopyrrolate is an anticholinergic drug that has been commonly used control peptic ulcers and to reduce severe or chronic drooling in pediatric patients with neurologic conditions (6). With the agreement between Catalent and Edenbridge, it is hoped that the proven drug can be reformulated into a novel drug platform to provide benefits to patient populations where fluid intake may be limited (5).

Another important aspect of improving patient adherence is that of preventing abuse of therapeutic products—an issue that has been at the forefront of efforts by pharma companies to tackle the opioid crisis. There are several re-formulated products currently available that feature abuse-deterrent properties.

To create an abuse-deterrent formulation, products can contain excipients that will form a gel if the product is tampered with, they can be formulated to be resistant to crushing or physical manipulation, or the formulation can include a sequestered antagonist (7). However, these abuse-deterrent formulations are limited in application as a result of the cost associated with them.

**Impact of COVID-19**

There have certainly been lots of instances of repurposing and reformulating drugs for the potential treatment of COVID-19. And, as was discussed in a recent article (8), vaccine developers are looking toward the inhaled route of administration to help ensure the needs of pediatric patients and those who fear needles can also be met in the fight to combat the virus.

Some other research in the area of pandemic response, however, has focused on nano-techniques. For example, recent work from researchers at the University of Liverpool’s Centre of Excellence for Long-acting Therapeutics (CELT) has assessed the potential of a nanoparticle formulation of niclosamide (NCL)—a cheap API that has been shown to be highly effective against SARS-CoV-2—to treat COVID-19 (9).

In the study, the CELT scientists used nanoprecipitation to form dispersible solid drug nanoparticle formulations of NCL, which means that the API did not require nanocarrier encapsulation and, as a result, did not suffer from limited drug loadings (9). The formulated NCL can be stored as a solid and then reconstituted with water to be used as a long-acting injectable. The study results showed that there was a sustained level of NCL in the plasma concentrations of rats for a 28-day period post-injection, which was administered once, intramuscularly (9). "Repurposing of medicines for SARS-CoV-2 has yielded mixed results, with some clear successes for immunomodulatory drugs such as dexamethasone, and work underway to repurpose drugs like favipiravir and molnupiravir that were designed for other viruses," said Professor Andrew Owen, a pharmacologist and co-director of CELT, in a press release about the study (10). “The ultimate utility of our long-acting injectable can only be determined in adequately powered and well controlled randomized clinical trials, but unlike other drugs that have been explored for repurposing niclosamide, target concentrations may be achievable in humans. The formulation has shown great promise in preclinical studies at a time when it is increasingly evident that drugs are urgently required to complement the vaccines.” “Repurposing drug compounds is much more than using existing medicines for a new disease,” added Professor Steve Rannard, a materials chemist and co-director of CELT, in the press release (10). “The existing active drug compound needs to be shown to be active at a significant level, then reformulated to address new challenges. The conventional route of administration may also not be relevant, and modifying the way the patient receives the drug compound is highly critical to efficacy.”

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Adopting Continuous Manufacturing for Solid-Dose Drug Products

Jennifer Markarian

Evolving equipment designs meet the unique needs of continuous processing techniques.

Continuous manufacturing (CM) has the potential to create higher quality drug substances and drug products, with greater flexibility in batch size and with a smaller facility footprint. The definition of what pharmaceutical manufacturers and regulators consider a “continuous process” is broad. The International Council for Harmonisation (ICH) Q13 draft guidance, which was released for public consultation July 27, 2021, gives examples of three concepts of CM: a combination or hybrid approach in which some unit operations run in batch mode while others are connected and run in a continuous manner; a process that makes either a drug substance or a drug product, with all unit operations integrated and running continuously; and an approach that connects both drug substance and drug product, in an end-to-end continuous process (1). The industry is making advances in all these methods, even the fully end-to-end system, with Continuous Pharmaceuticals receiving US-government funding in January 2021 to bring the company’s Integrated Continuous Manufacturing technology to commercial scale (2).

Powder-to-tablet equipment
Processes that are integrated to run continuously, from powder to tablet, have now been running commercially for more than five years, with the first oral solid-dosage drug made using continuous processing approved by FDA in 2015 (3). Since then, drug manufacturers, equipment suppliers, contract development and manufacturing organizations (CDMOs), and consortia of industry and academia have continued to innovate solutions to challenges such as equipment cleanability and better control of raw material feeders.

Commercially available CM equipment lines include entire systems as well as specific unit operations. GEA, for example, announced in June 2020 that it is making its well-established ConsiGma portfolio of CM equipment more accessible by allowing integration with third-party equipment and by defining ConsiGma 4.0 modules for individual unit operations (4). Standardized “off-the-shelf” elements also make CM equipment more affordable for a wider range of users.

Modular CM equipment is available from multiple suppliers. Glatt’s MOD-COS modular platform offers continuous processing beginning with powder feeding of API and excipients through coated tablets, with the addition of the Driam continuous Driaconti-T system for tablet coating added in 2018 (5).

L.B. Bohle offers CM equipment for a range of unit operations, including direct compression equipment, the QbCon WG continuous wet granulator and dryer, and a fully continuous (from powder to coated tablet) QbCon plant.

“Continuous wet granulation, drying, and milling equipment is already producing marketed products in Germany,” reports Robin Meier, manager of scientific operations at L.B. Bohle GmbH. “We also currently have a complete [powder to coated tablet] system being built right now, with factory acceptance testing planned for 2022.”

Meier suggests that, especially for companies with limited personnel resources, adopting a wet granulation process, from powder to milled granules, can be a good starting point for using CM and can be used to demonstrate the benefits of CM to stakeholders. “[Wet granulation] is easily controllable; it can be adopted quickly from already existing high-shear granulation processes and formulations, and [the company] can generate their first experience in continuous production.”

For example, Meier says that Bohle worked closely with a large German manufacturer of generic drug products to adapt a high-shear batch granulation process to continuous wet granulation and drying. The manufacturer
ON-DEMAND WEBCAST
Aired: Thursday, September 30, 2021

Event Overview

In vitro biochemical assays make possible the high-throughput screening (HTS) of large compound libraries. A successful HTS campaign is typically viewed as one that identifies large numbers of diverse chemical series hits as potential starting points on the way to a clinical candidate. These hits are typically weakly active in a primary screen and do not necessarily possess drug-like characteristics.

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Key Learning Objectives

- Identify what makes a promising starting point for a drug discovery program
- Learn strategies to more successfully triage hits
- Understand how to better focus efforts

Who Should Watch

- Drug discovery scientists
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was able to make product for the market within a few months after factory acceptance testing, says Meier.

When a CM process is up and running, in-line quality control measurements and process control systems with feedback loops can reduce the amount of out-of-specification product and improve quality. Training operators to understand the differences between batch and CM operation is one challenge. “One has to get used to the fact that most quality control of intermediate is running in-line or at-line, and that stopping a running CM line should be [avoided]. Sometimes it is better to discharge a few-hundred grams of product, [rather than] an intermediate stop of the whole line,” notes Meier.

Addressing feeding challenges
How materials are fed into the process is another significant difference between batch and continuous processes. In CM, loss-in-weight twin-screw feeders can be used to accurately dose raw materials as a continuous feedstream. “In a loss-in-weight feeder, the amount of weight lost is measured by means of a scale and sent back to the controller, which adjusts the speed of the screws to maintain a constant mass flow output,” explains Sharon Nowak, business development manager at Coperion K-Tron for Food & Pharmaceutical Industries.

Feeder designs are engineered to fit a process. “Since a variety of screw configurations exist that can also affect the amount of material per revolution of the screw, a variety of residence time distribution (RTD) models have been developed to look at overall feeder configuration (e.g., hopper size, type of screw, and screw speed) in order to predict the flow properties of different materials within the feeder and properly size the feeder,” says Nowak.

“The accuracy of feed is very much dependent upon screw fill,” continues Nowak. “Therefore, it is imperative that the material not only flow within the feeder hopper but also be entrained by the screws,” she explains. A challenge, however, is that some APIs and excipients do not flow easily and can be held up in the feed hopper. Developments in more flowable or coprocessed ingredients are one way to relieve flow issues, and equipment solutions are another.

Coperion K-Tron’s “smart” vibration device, the ActiFlow, monitors the loss-in-weight signal on the feeder controller; if there is an interruption in material flow, a vibration device is activated on the feed hopper to restart flow. “More importantly, this device is tied directly into the feeder’s control system and learns at what point in the process the material tends to bridge (due to changes in the feeder screw speed or feed factors). The ActiFlow proactively starts before the problem even occurs, and then it backs off on the vibration when the loss-in-weight signal is back in specification,” explains Nowak.

Equipment providers continue to improve digital load cell and feeder controls technology. For example, Coperion K-Tron’s newest load cells, combined with the company’s new KCM-III controller, have increased resolution to allow faster reaction time, which improves accuracy, especially at low feed rates and during setpoint changes or after a refill, says Nowak. “The refill reaction time is critical to maintaining overall accuracy in the continuous process,” she notes. The newest version of the controller also increases processing power and data storage capacity. These features are important for traceability and for tracking data trends. In the future, Nowak says, accelerometers could be used within the control system to accurately measure vibration and effects on feeder output, thus further increasing accuracy of control systems.

Another consideration for CM feeders is that users need equipment for very small feed rates, in the range of 10–100 g/h, as well as feeders designed for feed rates higher than 25–50 kg/h, says Nowak. “Coperion K-Tron has developed specific modular design feeders to handle a wider range of feed rate profiles. The use of specialty servo motors, for example, has widened the screw speed ranges available, with much higher turndowns, thus eliminating the requirements for changing gearboxes when higher or lower rate ranges are required.”

While this design allows higher rate ranges without a gearbox change, Nowak notes that the company’s QT model of feeders also uses a modular design, which is another advance that can facilitate quick changeovers in equipment. The overall designs, which include an option for quick roll-out frames on rails, have improved accessibility, added versatility, and minimized downtime, says Nowak.

“The QT model was specifically designed because of polling many of our key customers who were currently working in continuous processing, including continuous direct compression, continuous extrusion and granulation, and continuous coating,” says Nowak. “The new QT includes interchangeable modules that can be completely removed from the feeder motor/gearbox to change from one model to another. This allows the operator to easily remove everything in contact with the product in a few seconds and replace with either a new module or a different feeder model.”

Quick-change designs are also helpful for improving cleanability, which is a key area targeted for improvement by those involved in CM. Nowak says that Coperion K’Tron’s new designs have improved connections upstream and downstream of the feeder; fewer parts make assembly easier and faster. “Turntables and rails allow the feeder to be rolled back and turned 90 degrees from the feeder ‘cluster’, thus making access to change-out screws or perform other maintenance much easier,” says Nowak.

“The feeder is also automatically pitched 2 degrees for drainage to allow for quick wash-in-place operations.”

Equipment integration
Integration is another challenge for continuous processes, particularly when connecting equipment from different original equipment manufacturers (OEMs) for different pieces. “Many end users wish to remain with their existing, known unit technology,” says Nowak, so
communication between the unit operations is key. Nowak notes that, increasingly, OEMs and drug manufacturers are using OPC-UA as a common language. To make sure communication is clear and that the required parameters can be transmitted, Coperion K-Tron has partnered with several continuous systems integrators, such as Continua Process Systems, to ensure that communication and data collection of the complete process is seamless, says Nowak. The company’s KCM-III controller is equipped with communication cards and options for multiple protocols (e.g., Ethernet, Modbus, OPC-UA) so communication and integration into the overall process is maintained, she notes.

**Enabling adoption**

Innovations, such as these equipment improvements along with developments in control systems and materials, will assist solid-dosage drug manufacturers—from branded to over-the-counter and generic drugs—as they move ahead with adoption of continuous processes.

**References**


Unlocking the Power of 3D Absorbance Data

Peak deconvolution with photodiode array (PDA) detectors using a unique software function can separate peaks that are not resolved on-column, yield better detection results, and minimize method development and analysis time.

LCGC: What’s the difference between 2D UV-vis data and 3D PDA data?

DOMANSKI: Two-dimensional UV-vis data describes the total absorbance of a sample versus time for a single chosen wavelength producing a chromatogram. This type of data only shows that a compound has some absorbance at the wavelength of observation but can’t provide much more information. There is no way to tell if we are observing the compound at a wavelength of high or low absorbance or to predict what the compound might be. When we collect 3D PDA data, for each moment in time during the experiment, we can observe and record intensity across a range of wavelengths. This provides useful spectrum information that can determine maxima that yield the best limits of detection for the compounds of an assay or be used for traditional PDA data analysis such as cosine-vector peak purity.

LCGC: Beyond these uses, how does peak deconvolution unlock the full potential of PDA data?

DOMANSKI: While traditional PDA analysis tools may use a portion of the spectrum information available, peak deconvolution uses all the data and applies accepted mathematical techniques to separate peaks that are not resolved on-column. This can allow for detection of coeluting impurities in a potency assay, indicate an unexpected coeluting reaction product, or allow for characterization of a hard-to-separate degrader.

LCGC: What is the key to peak deconvolution, and how did this function get developed?

DOMANSKI: At the heart of our PDA peak deconvolution function is a sophisticated peak-fitting and spectrum-fitting algorithm that uses the multivariate curve resolution – alternating least squares (MCR-ALS) approach to determining solution sets, which is often used in benchtop spectroscopy applications such as chemometrics and observation of reaction kinetics. Because the technique can work with complex multi-component systems, it is ideal for LC-PDA data, where a single experiment may contain many peaks, each with associated
spectral data. Making the leap from accepted technique to implementation in software was done in conjunction with Eisai Co. Ltd., a leading global pharmaceutical manufacturer. Their goal was to accelerate therapeutic development by investing in technologies that would reduce analysis time and increase awareness of coeluion-related issues at every stage of the process.

**LCGC:** How does MCR-ALS deconvolution compare to other forms of peak purity assessment?

**DOMANSKI:** In contrast to traditional cosine-vector peak purity or purity-angle assessment, MCR-ALS deconvolution uses the entire data set from the defined time and wavelength domain to calculate peak shape and spectrum information for each identified chromatographic feature. If users have multiple impurities, up to five peaks can be identified within a single deconvolution segment, and up to 12 segments can be set in each chromatogram. So not only can coelution be spotted, but the potential impurities can be characterized with the same tools as any other peak, including the reconstructed spectrum.

**LCGC:** Can the deconvoluted peaks be integrated, and are reconstructed spectra accurate?

**DOMANSKI:** The short answers are yes, and yes. With regards to integration, we have studied a three-component system of common pharmaceutical drugs under ultra-high-performance liquid chromatography (UHPLC) conditions that result in partial separation and elution in less than 20 seconds. The resulting chromatogram produces peaks and valleys, but none of the peaks are baseline resolved. We then compared the results of PDA peak deconvolution with the traditional integration strategy of splitting the peaks with a vertical drop from the bottom of the valley to baseline and with separate injections of each standard.

Traditional valley-to-valley definition of the unresolved peaks led to as much as 13.1% deviation from the single standard injection, whereas using the deconvolution result, peak area was much more accurately assigned to the peaks, with the greatest error versus single standard injection being 5.6%. For the same three-component system, the reconstructed spectra were compared with the observed spectra from the single standard injections. For all the reconstructed spectra, the similarity was 0.9998 or greater, indicating a near perfect match to empirical data.

**LCGC:** With these capabilities, where do you see PDA peak deconvolution fitting into pharma and biopharma workflows?

**DOMANSKI:** With its ease of implementation, this technique can potentially replace complex multi-dimensional separation or time-consuming low-flow, high-capacity columns that cannot provide rapid results in a user-friendly way. As International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) and other regulatory bodies continue to tighten requirements for impurities detection, PDA peak deconvolution is an additional arrow in the quiver of analysis with its ability to detect low-level coeluting impurities. By identifying these species at the beginning of drug development, time can be saved throughout the downstream process. For early-stage high-throughput screening, PDA peak deconvolution could allow for faster injection cycles while maintaining the quality of data.

In a medicinal chemistry setting, deconvolution could be used in UHPLC reaction monitoring to look for hidden peaks or coeluting intermediates or be applied to re-injections of purification fractions as a secondary check of purity. As the drug-development cycle continues, any in-silico testing that uses absorbance can be augmented by using PDA peak deconvolution to provide information on coeluting peaks without the need to spend additional time on LC method development. And for groups that may have experience with PDA peak deconvolution, such as analytical method research and development, the ability to use this powerful technique integrated directly into the instrument software provides unprecedented access and ease.

**LCGC:** Is Shimadzu planning future development of this technique?

**DOMANSKI:** We are developing a new generation of the PDA peak deconvolution algorithm that will improve performance in terms of sensitivity and reliability for some of the most difficult use cases. Our international team is working in cooperation with pharma users to optimize the feature for lower detection limits, even when there is minimal on-column separation.

For more information, visit SolutionsForPharma.com.
Regulatory agencies require manufacturers to monitor pharmaceutical and biopharmaceutical product quality to ensure that a "state of control" is maintained throughout the lifecycle of new products and legacy products during the third process validation stage called continued process verification or ongoing process verification. To this purpose, manufacturers evaluate process data plotted on Shewhart control charts while scrutinizing them with Nelson rules.

Part 1 of this article series demonstrates, using real-world process data, that the four fundamental assumptions underlying the classical Shewhart control charts—randomness, independence, constant average, and constant variation—are often not met. Consequently, it is equally shown that applying traditional statistical process control (SPC) rules on pharmaceutical quality attributes and microbial environmental data leads to excessive false signal alarms, which in turn lead to futile investigations aimed at assigning causes to these potentially innocuous process deviations. Adopting a pragmatic approach aimed at relaxing the conventional SPC rules to minimize false alarms requires the correct interpretation of "state of control" in the context of the regulated pharmaceutical industry.

The European Union (EU) good manufacturing practice (GMP) (1) and FDA regulatory documents (2) require manufacturers to monitor pharmaceutical and biopharmaceutical product quality to ensure that a "state of control" is maintained throughout the lifecycle of new and legacy products during the third process validation stage called "continued process verification (CPV)" (2) or "ongoing process verification (OPV)" (1). Indeed, EU GMP Annex 15 clearly states that, "Manufacturers should monitor product quality to ensure that a state of control is maintained throughout the product lifecycle with the relevant process trends evaluated" (1). Thus, regulatory agencies expect manufacturers to implement a CPV/OPV plan.

The implementation of Stage 3 of the manufacturing process validation is translated into establishing an ongoing CPV/OPV program, which allows identification of CPV signals and defining types of responses to these signals. These CPV signals can in theory be detected by evaluating process data plotted on Shewhart charts, also called process-behavior charts (3), and scrutinizing them with Nelson rules (4), also referred to as detection rules (3) or runs tests in StatGraphics software (Stagraphics Technologies Inc., USA) program (Table I). However, the validity of these rules holds when the fundamental assumptions underlying the classical Shewhart control charts are met (5,6). Otherwise, applying traditional statistical process control (SPC) rules on real-world process data would lead to excessive false signal alarms, which in turn would lead to futile investigations aimed supposedly at assigning causes to these apparent process deviations.

This series of papers will review and demonstrate examples of pharmaceutical process data that the SPC fundamental conditions are often not met; explain the regulatory expectations regarding "state of control"; and suggest practical SPC tools that minimize false alarm signals.
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WHEN YOU NEED TO BE SURE

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It is shown that collecting, charting, and evaluating product and process data under relaxed and adjusted SPC rules allow a practical and streamlined implementation of the CPV/OPV program.

Why the fundamental SPC rules are not met

Manufacturers are likely to monitor data of process and in-process controls and of finished product (active substance or finished drug product), analytical method performance attributes (e.g., sample repeatability, chromatographic resolution and tailing factor, assays of QC samples), environmental data (e.g., particles in air, microbes in air, water, and on surfaces), and stability data. Figure 1 illustrates schematically how process data and attributes are monitored on control charts within preset upper and lower limits, under tolerance intervals delimited by specifications for quality attributes, by a normal operating range (NOR), a proven acceptable range (PAR), or a design space for process parameters and material attributes.

These data appear to be naturally amenable to evaluation with SPC techniques using Shewhart control charts. However, these control charts are based on the following basic assumptions: The data should:

- be random—one cannot know in advance what the exact outcome of an experiment will be
- be independent—two events are statistically independent if the occurrence of one does not affect the probability of the other
- have a constant process average
- have a constant process variation.

The applicability of the above assumptions was tested on examples of real pharmaceutical process data and are illustrated below.

Are data random and independent? Figure 2 shows a control chart of assay results of 100 batches of a drug substance (DS). This chart, as all other subsequent charts, was generated with StatGraphics Centurion XVIII software and is marked with a high number of asterisks, each indicating an application of one of the eight Nelson rules. A quick look reveals that the data are not random. This observation is contrasted with the lower trace in Figure 2, which reveals a totally different appearance of the same data set subjected to randomization (6) using a StatGraphics feature.

Furthermore, one can observe that some data are arranged in clusters of consecutive similar values. Thus, batches 8–12 as well as batches 33–40 are all high, but batches 46–53 are all low. This arrangement visibly negates the presence of data independence. This behavior is typical of a phenomenon called positive autocorrelation whereby a smaller value tends to follow a smaller one and a higher value tends similarly to follow a higher one. This situation can in principle be explained by manufacturing of several consecutive batches under underlying similar conditions, such as using the same lot of reagent or the same lot of an active ingredient, the same production machine, same production line, same time laps, or the same operators. These conditions may change in a subsequent group of manufactured batches. Indeed, manufacturing in campaigns is often practiced in the pharmaceutical industry. Statistically speaking, autocorrelation is a correlation between a set of data and its copy delayed by one or more data points as a function of the delay number (or time lag). In other words, autocorrelation reflects the similarity between observations as a function of the time lag between them (similarity at any time delay is highest when equal

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**Table I. Nelson rules for detecting special causes in control charts.**

<table>
<thead>
<tr>
<th>Nelson rule #</th>
<th>Runs test per StatGraphics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Beyond-3sigma-limits run</td>
</tr>
<tr>
<td>2</td>
<td>A Runs above or below centerline of length 9 or greater.</td>
</tr>
<tr>
<td>3</td>
<td>B Runs up or down of length 6 or greater.</td>
</tr>
<tr>
<td>6</td>
<td>C Sets of 5 observations with at least 4 beyond 1.0 sigma.</td>
</tr>
<tr>
<td>5</td>
<td>D Sets of 3 observations with at least 2 beyond 2.0 sigma.</td>
</tr>
<tr>
<td>7</td>
<td>E Sets of 15 observations at or within 1.0 sigma.</td>
</tr>
<tr>
<td>8</td>
<td>F Sets of 8 observations beyond 1.0 sigma.</td>
</tr>
<tr>
<td>4</td>
<td>G Sets of 14 observations alternating up and down</td>
</tr>
</tbody>
</table>

**Figure 1:** Schematic presentation of statistical process implementation within the regulatory requirements. PAR is proven acceptable range, IPC is in-process control, NOR is normal operating range, LCL is lower control limit, UCL is upper control limit.
to one or non-existent [i.e., data is random] when equal to zero). If data are non-random, then one or more of the autocorrelations will be significantly non-zero. The autocorrelation chart (not shown) of the drug substance assay values reveals large statistically significant coefficients of the first two lags (0.73 and 0.47), implying that data are definitely not random or independent.

**Should the data be normal?** It is not surprising to state that process data are often not normally distributed, as illustrated in the skewed histograms of the quality attributes of the 100 batches of the drug substance (DS): assay, contents of a related impurity and water, and a specific rotation (Figure 3). All four p-values of the Shapiro-Wilks and Anderson-Darling normality tests are well below 0.05, confirming indeed that all data sets are non-normal. Often, one would draw control charts with either of the data sets and evaluate the process behavior with Nelson rules (Table I). Since most Nelson rules are based on Gaussian data distribution, excessive applications of these rules are often encountered. Figure 2 reveals 67 flagged unusual runs by Nelson rules 2–8 and 17 beyond-limits (rule 1).

Nelson rule 1—a point beyond the three-sigma limit—is still subject to a common misunderstanding. It is well known that 3-sigma limits cover 99.73% of data of a normal distribution. While many think that data needs to be normally distributed, Shewhart did not make that requirement (7). He set the control limits to be 3 sigma-limits as empirical.

---

**Figure 2:** Charts of assay (% w/w) of batches of a chemical drug substance before (upper) and after randomization (lower).

**Figure 3:** Histograms of several quality attributes of a chemical drug substance (as say, water content, specific rotation, and impurity content). All histograms appear to be non-normally distributed.
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limits, which encompass the vast majority of data (close to 100%). Wheeler demonstrated that 3 sigma-limits cover at least 97.5% of all data coming from a variety of non-normal distributions (8). Thus, if one accepts that up to 2.5% of process data can exceed the 3 sigma-limits (Nelson rule 1), then the fit to a normal distribution is not a requirement. However, when data distribution is heavy-tailed and data are generated in abundance, such as environmental monitoring data that is collected on a daily, weekly, or monthly basis, one may encounter an unacceptably large number of 3-sigma beyond-limits events (even more than 2.5%) that would need to be reported and investigated. Figure 4 shows an example of a non-normal distribution of 359 microbial counts in air (cfu/m³) measured in a classified D room as well as a control chart flagged with 19 beyond-limits (5.3%).

Of course, one can attempt to normalize data via some mathematical transformation. However, the author prefers the use of the original data as is and endorses Wheeler's view, whereby non-linear transformations can lead to a loss of the physical meaning of the original data, distort the data, hide the signals, and possibly change the results of the analysis (7).

Are the process average and variation constant? A stable and predictable process is expected to operate with a constant process average that is subject to one source of variation. When an individual Xbar-R chart is constructed from positively autocorrelated measurements, the presence of clusters of high similar values and low similar values may be interpreted as temporary shifts of the process average. This autocorrelation in turn is a demonstration of non-constant process average. When the short-term variation is derived from closely similar values of the clusters, the resulting standard deviation is inevitably smaller, thus leading to narrower control limits and ultimately, to a large number of beyond-limits. Figure 2 indeed shows a considerable number of 17 values beyond the lower and upper control limits from 100 data points (i.e., 17%). These are in fact false signals.

Similarly, an Xbar-R or Xbar-S chart of grouped data can exhibit excessive beyond-limits values when a process is operating with more than one source of variation. When a process can inherently vary from subgroup to subgroup, the variation within the subgroup may be smaller than that across the subgroups. Recognizing the presence of an additional source of variation is based on a deep acquaintance with the behavior of the process in question and the context of the data. When the data have more than one level of background variation, one cannot always use the within-subgroup variation to compute appropriate limits for the subgroup averages (9). If this additional variation source is ignored, control limits will be calculated from the smaller within-subgroup variation, thus also leading to excessive beyond-limits values. An example of such behavior is depicted in Figure 5 which plots microbial counts in air (cfu/m³) of a Class C room, sampled from four locations at each sampling time. The lower trace of Figure 5 displays a scatterplot of the four counts at each sampling time, and the upper trace shows the 95% confidence intervals of the means of individual subgroups. This upper trace reveals that a considerable number of intervals do not overlap among others, thus indicating a non-constant process average. This divergence of the subgroup averages is further supported by the outcome of a one-way analysis of variance (ANOVA) made on the 105 subgroups. The resulting p-value of the F-test is less than 0.05, suggesting also a statistically significant difference between some means from one week to another at the 95.0% confidence level. Considering the context of these microbial counts recorded mostly on a weekly basis, one can definitely rationalize that the contamination level in the same room may well vary from one sampling time to the next one. So, in addition to the within-week variation, there is an additional across-week variation. Therefore, when this additional source of variation is ignored, a conventional Xbar-R chart generated with these data (Figure 6) expectedly shows a high number of 25 beyond-limits events in the Xbar plot.

Regulatory interpretation of state of control

Data from pharmaceutical manufacturing—data of in-process controls and finished product, process parameters, environmental monitoring counts of microbes and particles, and analytical method performance parameters—are in principle amenable to charting on Shewhart Control Charts and evaluation with Nelson rules (4) for detecting trends and shifts in process average and variation. However, as previously seen, applying traditional SPC rules on pharmaceutical quality attributes and microbial environmental data leads to excessive false signal alarms, which in turn leads to futile investigations aimed supposedly at assigning causes to these apparent and innocuous process deviations. Thus, a different practical approach for minimizing the false alarms rate is called for and at the foundation of this pragmatic approach, lies an understanding of the context of the pharmaceutical process data and the regulations governing this industry.

“State of control” versus “state of statistical control.” SPC methodology employs the eight Nelson rules to evaluate process data for detecting trends and shifts in process behavior in view of establishing whether the process is operating under common cause or under special (or assignable) cause variation. Implementing these tools allows one to separate the signal from the noise and determine if the process is under a “state of statistical control”.

A process in a state of statistical control is operating with only chance causes of variation. A process that is operating in the presence of assignable causes is said to be out of control (10). Interestingly, regulatory documents (1,2) do not mention nor require statistical control. Instead, regulatory documents call for a state of control, which EU GMP Annex 15 defines as “a condition in which the set of controls consistently provides assurance of acceptable process performance and product quality” (1). This definition reflects a pragmatic and flexible approach whereby a manufacturer who judges his process performance and his product quality as consistently satisfactory over time is in fact maintaining his process in a state of control. This approach opens the door to possibilities of relaxing and adjusting the traditional SPC rules to a given process for the purpose of declaring it as operating under control.

“Action limit” versus “control limit.” SPC methodology sets statistically derived control limits as multiples of process sigma: 3-sigma
Figure 4: Histogram of microbial counts (cfu/m³) of air samples recorded in Class D room (upper) and X-chart of the same data with control limits based on 3 sigma (lower). Nineteen data points are flagged as beyond-limit events.

Figure 5: Confidence intervals of the means of groups of four microbial counts (cfu/m³) recorded at each sampling time in Class C room (upper) and scatterplot of the same data (lower).
control limits (upper and lower), 2- and 1-sigma-limits (called also outward and inner warning limits, respectively). These limits, in principle, delineate probabilities of occurrence of a data point located as 3, 2, or 1 sigma away from the process average. However, the regulator is interested in reaction-driven limits—an alert limit and action limit—with the intent to react in a timely manner and determine the need for action to ensure and document that the process is maintained in a state of control (1,2). The former is a breach that should trigger a review and follow-up, which might include investigation and corrective action. The latter is a breach that should lead to a root cause investigation and risk assessment. Indeed, the FDA guide on process validation (2) and the EU GMP Part II (11) explicitly call to set appropriate alert limits and action limits, and the new draft EU GMP Annex 1 calls to set alert levels and action limits for the counts of viable and non-viable particle monitoring (12).

Regulatory approach versus SPC approach. The manufacturer now needs to decide which specific Nelson rule is considered a signal for an alert or for an action. An SPC-oriented approach concentrates solely on the behavior of the process data and generates flags that signal a likely or actual deviation of the process from its state of statistical control. Some statisticians do not favor designating specifications on a control chart, because specification limits represent the “voice of the customer” (or regulator) while the control limits represent the “voice of the process”. In contrast, regulations (1,2,11,12) call for applying a risk-based approach, and this implies paying attention also to the process capability, hence to the specification limits as well. For instance, a well-behaved process under statistical control that has a 3-sigma control limit close to an upper specification limit is nevertheless considered by a regulator to be a risky process. The regulatory approach considers simultaneously both the state of control and the capability of a process, which again reflects a pragmatic approach to the overall monitoring of a manufacturing process. Figure 7 illustrates how manufacturers can integrate the SPC into their practice. The upper
control chart depicts the classical SPC approach with a 2-sigma limit as a warning limit and the 3-sigma limit as an upper control limit (UCL). The specification is not shown. When establishing alert and action levels, manufacturers may establish a two- or three-tier approach (13). Some manufactures may adopt a three-tier approach whereby the 2-sigma limit becomes an alert limit, the UCL is an action limit, and a specification (for individual data) is added to the chart. Others adopt the simpler two-tier approach whereby the 2-sigma limit is ignored, the UCL becomes an alert limit, and the specification/regulatory limit is an action limit. The two-tier approach is often applied in monitoring environmental counts of microbes and particles in classified cleanrooms.

**Conclusion**

Real-life data of pharmaceutical and microbial counts in classified rooms were shown to confirm that the four fundamental requirements of conventional Shewhart control charts—randomness, independence, constant average, and variation—are often not met. Furthermore, process data are often shown to be non-normal. Under these conditions, process deviations along with a considerable number of false beyond-3-sigma limits are detected with Nelson rules. Adopting a pragmatic approach aimed at relaxing the conventional SPC rules requires the correct interpretation of state of control in the context of the pharmaceutical industry.

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The purpose of stability testing programs is to ensure a drug product’s safety and efficacy remains within its specifications throughout the shelf-life. To develop suitable analytical methods to detect and quantify degradation products, drug manufacturers should conduct forced-degradation studies.

“Conduct proper analytical method development by understanding the drug substance degradation pathway,” says Shailesh Vengurlekar, SVP, quality and regulatory affairs, LGM Pharma. “Use validated stability-indicating test methods to perform testing at the scheduled time period.”

Stability programs and their practices can vary widely. These differences become more intricate when comparing stability testing of small molecules versus biologic drugs and how it impacts shelf life.

“A larger company that manufactures multiple products and batches must manage numerous stability studies with many more samples to analyze,” says Patrick Nieuwenhuizen, senior manager consultant, PharmaLex. “It can be more challenging to manage the volume of samples and testing compared to a smaller company with fewer products and fewer studies. Hence, you see larger companies are making more use of integrated software programs that can manage multiple stability studies.”

Regardless of company size, there are essential practices for stability testing that all companies should implement. From study design to testing completion, all companies should have a clearly defined process for stability, explains Anna Thabit-Jones, stability manager, PCI Pharma Services. To set up and manage a stability study, a detailed protocol is essential.

Nieuwenhuizen also notes that having a robust stability program is an essential practice for stability testing and shelf life. In addition, companies should have a scheduling system in place with adherence to testing the allocated time points within the study. There are many examples of companies receiving a regulatory citation for not having their stability program organized how it should be, Nieuwenhuizen adds.

According to Vengurlekar, all companies should follow the International Council for Harmonisation (ICH) guidelines to design a proper stability program and testing intervals.

Anis H. Khimani, PhD, senior strategy leader, pharma development, life science, PerkinElmer adds, “ICH Q1E guideline provides recommendations on how to use stability data generated in accordance with the principles detailed in the ICH guideline, Q1A(R2) Stability Testing of New Drug Substances and Products, to propose a retest period or shelf life in a registration application.”

For recommendations on the setting and justification of acceptance criteria, reference ICH Q6A and Q6B, Khimani specifies, whereas ICH Q1D is for the use of full- versus reduced-design studies.

Both small and large pharma organizations should consider addressing the critical quality attributes (CQAs),continues Khimani. CQAs could have an impact on purity, potency, drug release, stability, and safety. But for both small-molecule and biologic drugs, a quality assurance review of protocols and establishment of methods and validation should be done. Khimani also confirms that a typical study can last up to two years based on the storage conditions and expected shelf life.

“A consistent and appropriate maintenance/calibration program for the stability chambers is also essential,”
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Thabit-Jones adds. “If you can’t trust your chambers to be working correctly and operating at the required temperature and humidity, then you can’t trust the data generated for any products stored. Depending on the size of the company’s stability program, effective sample inventory is also key to maintaining sample integrity. Testing should be conducted as soon as possible following the removal of the samples from the stability chamber. This is particularly important at the earlier time-points and for accelerated conditions, as you want to capture the product stability at that point. Further degradation can occur over time.”

**Stability programs and their practices can vary widely.**

**Stability testing for small-molecule vs. biologic drugs**

Although there are similarities in stability testing between small-molecule drugs and biologics, there are distinct differences as well.

“Issues associated with instability are potentially more significant and perhaps more likely to be observed with biologics than their small-molecule counterparts,” says Vengurlekar. “Biologics have a tendency to aggregate and are prone to degradation. Thus, the methods to accurately quantify drug substance degradation differs between small-molecule and biologic drugs. To monitor various degradants from biologics, typically, analytical techniques such as Fourier-transform infrared, nuclear magnetic resonance, chromatography, mass spectrometry, and electrophoresis are used.”

Furthermore, stability tests are performed under controlled conditions (temperature and humidity) that match how the drug will be stored, which differ for small-molecule drugs and biologics.

“One of the biggest misconceptions of stability testing is that small-molecule drugs and biologics, stability programs for biologics are far more complex, confirms Srivastava. “This is due to the complexity, degradation pathway, and mechanism of action differences between the two drug modalities,” Srivastava continues. “The degradation mechanism for small-molecule drugs is simple, typically involving hydrolysis and oxidation. Biologics, in comparison, can undergo a variety of physical and chemical degradation mechanisms, including unfolding, aggregation, fragmentation, surface absorption, particulate oxidation, deamidation, hydrolysis, and disulfide exchange. Additionally, the potency can be extrapolated from

**Misconceptions of stability testing: small-molecule vs. biologic drugs**

One of the biggest misconceptions in stability testing—especially for late clinical or commercial products—is that the stability tests will produce a clear trend, notes Thabit-Jones, which is flat, increasing, or decreasing over time. However, some products may produce variable data points at each testing time-point and may not produce a clear trend until much later in the study.

**One of the biggest misconceptions is that stability testing is routine.**

“This makes it difficult to assess the likelihood of meeting the required shelf-life early on, and a deeper review of historical data can be required to support conclusions,” Thabit-Jones continues. “In addition, stability testing can sometimes be an ‘afterthought’ for some companies, but it is critical to collect data about product stability early on. The more data available, the easier it is to assess and investigate data that may be out of specification, out of trend, or out of expectation at later stages in the product lifecycle.”

Another misconception is that stability testing is routine. While the testing techniques themselves are routine, every study is different and requires different testing, time-points, conditions, and final assessment, Thabit-Jones adds. Although some people may perceive stability testing programs as similar for small-molecule drugs and biologics, stability programs for biologics are far more complex, confirms Srivastava.

Contin. on page 56
Characterization and Monitoring of Cell Therapy Attributes Using Mass Spectrometry

Register for this free webcast at: www.pharmtech.com/pt_p/cells

Event Overview

Cell therapeutics are far more complex than traditional protein biologics, requiring comprehensive understanding of the biochemical architecture to define product quality attributes and optimize the development and manufacturing processes. High-resolution mass spectrometry (MS) enables scientists to obtain system-wide insight at molecular level as the cells undergo gene transfer and expansion. Learn how novel MS approaches are developed to characterize and monitor cell therapy attributes at Bristol Myers Squibb.

Key Learning Objectives

• Current challenges in cell therapy attribute characterization
• Novel mass spectrometry workflows for cell therapy attribute characterization and monitoring
• Future applications of mass spectrometry in cell therapy

Who Should Watch

• Directors, lab managers, scientists supporting analytical development of cell therapy programs.

For questions email kbarry@mjh lifesiences.com
Public Trust in Medicine
Quality as Public Health Challenges Emerge

Jaap Venema and Jennifer Devine

Public health challenges have highlighted the need for agility in maintaining the quality of medicines. Patient and consumer trust in medicines and public confidence in their quality and availability are critical for positive health outcomes. When systems for safeguarding medicines are weakened, public trust erodes.

Emerging public health challenges—including global vaccinations to stop the spread of COVID-19, proliferation of substandard and falsified medicines amid demand surges, and the detection of potentially cancer-causing nitrosamine impurities in some commonly-used medicines—have underscored the need for agility in maintaining the quality and consistency of medicines. The US Pharmacopeia (USP) continues to build trust in medicines by creating scientific standards, tools, and solutions for industry, regulators, and practitioners that promote the ongoing availability and reliability of quality medicines in response to public health crises and other health needs.

An ongoing response to COVID-19
Hand sanitizers and methanol contamination. In 2020, the demand for alcohol-based hand sanitizers had surpassed its supply due to the rapidly evolving COVID-19 pandemic. As shortages of hand sanitizer became widely reported, compounding pharmacists and non-traditional manufacturers, including distillers, began making alcohol-based hand sanitizer for the public. USP scientists and other experts came together to develop a hand sanitizer toolkit that included quality standards for sanitizer ingredients and resources for compounding alcohol-based sanitizer.

By July 2020, FDA alerted the public to a sharp increase in hand sanitizer products that were labeled to contain ethanol (also known as ethyl alcohol) but tested positive for methanol contamination. Methanol, or wood alcohol, is a substance that can be toxic when absorbed through the skin and can be life-threatening when inadvertently ingested. Recognizing that methanol-contaminated ethanol had entered global supply chains—for both hand sanitizer products as well as other medicines—USP collaborated with FDA and stakeholders to update USP monographs for Alcohol and Dehydrated Alcohol in the United States Pharmacopeia—National Formulary (USP–NF) to include a specific identification test to detect and control methanol contaminants. Using the Accelerated Revision Process, USP posted these revisions on Aug. 17, 2020, which then became official on Sept. 1, 2020. USP and FDA worked together to communicate these changes to stakeholders. A virtual open forum was held with panelists from USP, FDA, and industry on regulatory and compendial requirements for producing alcohol used in drug products. USP also held global seminars on helping to ensure quality alcohol-based hand sanitizer production and safe use. The seminars were tailored to meet the needs of manufacturers and healthcare practitioners in the United States, Latin America, India, and Africa.

USP published Revision Bulletins for its monographs for Isopropyl Alcohol and Azeotropic Isopropyl Alcohol on July 30, 2021, which will become official on Feb. 1, 2022. The six-month window gives stakeholders additional time to implement changes introduced in the Limit of Volatile Impurities test, including the addition of methanol as a specified impurity.

Proper vaccine handling. As vaccines to combat COVID-19 were authorized for use in the US in early 2021, USP mobilized efforts to help get shots in arms by...
ON-DEMAND WEBCAST
Aired: Tuesday, October 5, 2021

Presenters

Sean Diver
Director, Commercial Development, North America at Lonza

Jason Bertola
Head of Commercial Development, North America at Lonza

Moderator

Rita Peters
Editorial Director, BioPharm International

Working as One to Advance Your HPAPI to Market

Event Overview
Creating the optimal pathway for your HPAPI small-molecule drug candidate through each clinical phase is critical to your success.

This webinar explains how to choose the right partner with the right expertise for your HPAPI development journey, from early phase to commercialization through innovation in manufacturing technology and flexible business models.

Supported by a case study, we show how Lonza has developed an innovative production offering to accelerate development and provide a more flexible (HP)API supply for customers through the full product lifecycle.

Key Learning Objectives

• Accelerate your speed to clinic
• Optimize your manufacturing process (?)
  o Safely managing your HPAPI molecule and de-risking exposure
• Optimize your commercialization strategy with proven experience

Who Should Attend

• CMC Directors
• COO or CEO of small Biotech
• CMC Consultants
• Head of Drug Substance External Manufacturing
• Head of Supply Chain and Technical Operations
• HPAPI experts
• Commercial Representatives

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developing resources for the healthcare practitioner community. USP’s COVID-19 Vaccine Handling Toolkit addressed operational considerations for healthcare workers administering vaccines and potential efficiency gaps at mass vaccination clinics across the US. Developed by dozens of experts from multiple disciplines and areas of practice—including healthcare practitioners, FDA, and the Centers for Disease Control and Prevention—the toolkit helps practitioners safely and efficiently prepare and transport the Moderna, Pfizer-BioNTech, and Johnson & Johnson/Janssen vaccines while also ensuring vaccine integrity and provides best practices for vaccine waste minimization. The availability of USP’s toolkit has led to an estimated increase in supply of more than 53 million doses of vaccines by optimizing the number of vaccine doses withdrawn from vials, resulting in an estimate of 26.5 million more people vaccinated (1).

In July 2021, USP released the International COVID-19 Vaccine Guide for healthcare practitioners outside of the US. Based on the COVID-19 Vaccine Handling Toolkit, this guide provides information on several COVID-19 vaccines used internationally. It highlights operational considerations about vaccine preparation, transport, and handling unique to geographies outside of the US and includes a Visual Inspection Guide to help identify falsified COVID-19 vaccines.

Substandard and falsified vaccines. High global demand and insufficient supply have resulted in the vastly inequitable global distribution of COVID-19 vaccines, and these factors also have created economic incentives for the deliberate falsification of vaccines. The issue of substandard and falsified COVID-19 vaccines will likely remain a problem for several years to come as the world continues to work toward immunization of the global population. While the World Health Organization advises that vaccines procured from assured sources should not be tested again by receiving countries, as they have been tested and released already by National Regulatory Authorities (2), individual countries or manufacturers may have a need to develop their own laboratory capacity for the testing of COVID-19 vaccines.

To support manufacturer and regulatory laboratories that need to develop and validate assays for assessing quality attributes of vaccines, USP created toolkits to help users navigate relevant documentary standards in USP–NF. These Vaccine Quality Attributes toolkits are organized based on the various COVID-19 vaccine platforms currently in use for authorized and approved COVID-19 vaccines. The toolkits include common quality tests, standards, and other information to support development and validation of analytical tests commonly used to help ensure the quality of vaccines. These toolkits can help reduce risks from substandard and falsified vaccines and, ultimately, increase public trust.

Nitrosamine impurities in medicine supply chains

Before the emergence of COVID-19, concerns about the global medicine supply chain had already been raised when unacceptable levels of a potentially-cancer causing nitrosamine impurity was found in the blood pressure medicine, valsartan. Extensive investigations determined that nitrosamines were caused by a change in the manufacturing process that had been made to improve product yield.

Nitrosamines can arise throughout the drug manufacturing process, including synthesis, purification, formulation, packaging, and storage. Even small changes to manufacturing processes can introduce new or changing levels of impurities. They can be introduced in raw materials, solvents, or result from product degradation. With so many possible sources for nitrosamine impurities, manufacturers should establish control strategies to evaluate and mitigate potential risks. When the risk of nitrosamines is identified, the use of analytical testing to detect and measure nitrosamine levels is vital to protect patients from exposure to unacceptable levels of these potentially harmful substances.

USP responded to the nitrosamines impurities crisis with solutions to detect and measure nitrosamine levels. This work has been advanced by USP’s committee of volunteer experts comprised of industry scientists, global regulators, and other stakeholders with expertise in manufacturing and organic impurities. Taking a multi-pronged approach, USP has developed nitrosamine reference standards, a general chapter on nitrosamine impurities, and other resources and information that support manufacturers as they take proactive measures to prevent exposing patients to potentially harmful nitrosamine impurities.

USP General Chapter <1469> Nitrosamine Impurities was published in USP–NF in June 2021 and becomes official on Dec. 1, 2021. The general chapter identifies possible sources of nitrosamines in drug products, their components, and their manufacturing process, along with the risks associated with each source. The general chapter provides recommendations on nitrosamines risk assessment and the development of detection and control strategies. If manufacturers detect nitrosamines in their products, the chapter provides a range of different test methods for quantifying them to help ensure they remain below harmful levels.

USP’s nitrosamine Reference Standards can be used by manufacturers as controls to test against their own materials. USP’s general chapter includes methods for using the nitrosamine Reference Standards. The Reference Standards may also be used with methods provided by FDA and other regulators as well as for validating methods developed in-house.

Regulators expect manufacturers of APIs, marketed products, and pending new products to conduct risk assessments for nitrosamine impurities, take mitigative actions if these impurities are detected, and report any changes implemented to prevent/reduce these impurities.

In addition, USP has launched Nitrosamines Exchange—a new online community focused on nitrosamines risk assessment. Nitrosamines Exchange is a dynamic forum for members of the pharmaceutical community to come together and exchange ideas, share insights, and learn from one another about the science of nitrosamines and the development of
Event Overview:
Join global industry and regulatory experts as they discuss current extractables and leachables (E&L) hot topics on pharmaceuticals, biopharmaceuticals, and medical devices. Extractables and leachables are an important consideration when developing medical products and devices. This conference will give you an insight into a number of different topics within the ever-changing world of E&L.

Moderator: Dr Andrew Feilden, European E&L Strategic Director, Hall Analytical

Key Learning Objectives:
• Gain insight to some of the important E&L areas for medical devices and pharmaceutical products
• Learn about some of the key challenges within the field of E&L
• Understand the science behind the testing

Who Should Attend:
• Representatives from the supply chain to pharma, biopharma, and medical devices
• Members of the medical and medicinal product world wanting to know more about the challenges with E&L
• Those new to the field of E&L wanting to learn some key aspects of the requirements

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null
exposure of the downstream portions of the sterile product transport line poses a risk to maintaining the sterility of the filtered product. This, along with other risks, including additional interventions in the aseptic space, increased complexity of the filtration system, execution of this additional tests, failure of PUPSIT assembly components and stress on sterilized filter to perform the test, is greater than the remote likelihood of microbiological contamination from a flaw which can be masked during use of the filter that is not detected afterwards” (1).

As indicated above, the PUPSIT concept is actively being debated. The best way to address the use/non-use of PUPSIT in your organization is to make sure you have an appropriate risk assessment in place defending your position.

Q. What makes aseptic drug manufacturing so challenging?

A. Aseptic manufacturing requires highly trained and experienced people to carry out the operations, special equipment, and cleaning procedures, and constant environmental monitoring even when the manufacturing area is not in use. The risk to the product and the patients is significant if the aseptic process is compromised.

Reference
The Basics of Aseptic Processing

Susan J. Schniepp, distinguished fellow at Regulatory Compliance Associates, answers some commonly asked questions about aseptic processing.

**Q.** What is aseptic processing?

**A.** Aseptic processing is a manufacturing method that can produce product that is absent of bacteria without subjecting the product to terminal sterilization processes. Many products degrade and become ineffective when subjected to the harsh conditions of terminal sterilization. Aseptic process manufacturing allows these products to be produced in a sterile environment, allowing them to maintain their effectiveness while being safe to inject into patients.

**Q.** What is the difference between aseptic processing and terminal sterilization?

**A.** The major difference between aseptic processing and terminal sterilization is when the sterilization step occurs in the process. In terminal sterilization, the sterilization is performed after the API, excipients, containers, and stoppers have been assembled. The assembled product is then subjected to high heat and/or radiation that renders the final product sterile. Terminal sterilization processes are harsh and can have negative effects on the efficacy of the product. For products that can’t withstand terminal sterilization, manufacturers employ aseptic manufacturing. The aseptic manufacturing process requires the drug product and any excipients, the container, and the stoppers to be individually sterilized before being introduced into the cleanroom or sterile manufacturing core where the final product is manufactured in a highly controlled environment constantly monitored for air quality and potential microbial ingress.

**Q.** Why must manufacturers establish environmental controls for aseptic processes?

**A.** Let’s be clear, all drug manufacturing, including solid oral dosage form and terminal sterilization manufacturing are required to have established environmental controls. This requirement is addressed in global current good manufacturing practices (cGMPs). The purpose of these controls is to prevent product contamination due to insanitary conditions. The environmental controls to be monitored include, but are not necessarily limited to, air quality including particulate matter, ventilation, temperature, humidity, air pressure, and microbial contamination. The environmental control limits are, as expected, stricter for aseptic processing manufacturers due to the nature of their business.

**Q.** What does PUPSIT stand for, and why is it required?

**A.** PUPSIT is a term used in aseptic processing operations, and it stands for pre-use post-sterilization integrity testing. This testing is performed on the sterilizing filter after it is installed before product manufacturing and then again after the product manufacturing is completed. The purpose of the pre-test is to ensure that the sterilization and installation process has not damaged your filter prior to the filtration of your product. The purpose of the post-test is to demonstrate that the filter remained intact and undamaged during the actual filtration of the product.

An article published by the Parenteral Drug Association (PDA) states, “Since 1998, the EU Guidelines to Good Manufacturing Practice: Medicinal Products for Human and Veterinary Use, Annex 1 (Manufacture of Sterile Medicinal Products) or ‘Annex 1’ has contained the requirement for verifying the integrity of a sterilizing grade filter before use and after its sterilization. The requirement remained in the 2008 revision and in the 2017 draft revision to Annex 1. While not a requirement by the U.S. FDA, EMA inspectors and some PIC/S inspectors have been increasingly expressing expectations for companies to employ this testing procedure” (1). The article goes on to explain the concerns that led to the PUPSIT requirement: “Concerns have been raised that a sterilizing filter could develop certain flaws that would allow microbiological contamination to pass during filtration. The key is that flaws may be blocked or clogged by fluid contaminants or components during the filtration process and remain undiscovered during post-use integrity test. This phenomenon is sometimes referred to as “filter flaw masking” (1).

Additionally, the article explores the rational for not employing PUPSIT because of the concern “that the contamination/product deterioration risk associated with performing PUPSIT may greatly outweigh the risk of product contamination as a result of the masking effect. To test a filter that has been sterilized by current means, the sterile filtrate side of the sterilized filter must be under atmospheric pressure, requiring a fluid pathway to remove any wetting agent. The
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