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On the cover

COVER STORY

16 Paradigm Shift for Data Analysis and Interpretation

Leveraging vast quantities of analytical data requires digitalization and platform integration.

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FEATURES

Continued on page 8

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Continued from page 6

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As Drug Spending Slows, Investment Must Pick Up

Rita C. Peters

Biosimilars, pricing strategies, and technology will influence growth in spending on drugs.

An annual report from the IQVIA Institute for Human Data Science Study (1) predicts slower growth in drug spending, outlines the need for technology adoption, and warns about implications for emerging therapies and policy decisions. The report, issued in late January 2019, noted that global drug spending reached $1.2 trillion in 2018 and is expected to top $1.5 trillion by 2023. While spending is predicted to continue to grow, the increase will be at a slower pace than previous years. The projected 2023 spending level, up 50% from 2016, will be accomplished despite lower growth of 3–6% on an annual compound basis compared to 6.3% over the past five years.

The United States and pharmerging markets will drive growth over the next five years with 4–7% and 5–8% compound annual growth, respectively, the study reports. However, growth in the top-five European markets will be 1–4%, compared with 3.8% in the past five years; Japan's predicted topline growth is -3–0%. Growth in China is expected to slow to 3–6%.

Growth triggers and traps

Through 2023, IQVIA expects FDA to approve, on average, 54 novel drugs per year, up from an average of 46 drugs in the past five years. The annual average spending in developed markets on new brands is expected to rise slightly to $45.8 billion in the next five years.

Patent expirations, generic and new drug competition, and drug pricing pressures will contribute to slower growth, however. Competition from biosimilars in 2023 is predicted to be three times the level it is today; and half of spending on medicines will be for specialty drug products. Net manufacturer revenue will grow at 2–3% in 2019, down from a high of 10.3% in 2014.

The loss of exclusivity of branded drug products is forecasted to be $31.5 billion in developed markets in 2019; the forecast impact through 2023 is $121 billion, including almost $17 billion for biologics. In the US, the impact will be $95 billion through 2023, with $15.8 billion for biologics.

The US will continue to lag other developed markets in adoption of biosimilars; however, the report authors expect US policymakers to push for more biosimilar adoption by addressing reimbursement policies, perhaps in time for adalimumab biosimilars in 2023.

Influential factors

The report also identified key factors that will influence healthcare costs including the use of machine learning and artificial intelligence to identify drug targets and monitor clinical trials, use of real-world evidence in clinical trials, a greater voice for patients in the development and administration of drugs, and pricing reforms. Other predictions include the following:

- Large pharma companies will increase investment in technologies and operational efficiencies.
- Emerging biopharma companies will represent a greater share of new drug launches. Big pharma companies will partner with smaller companies rather than acquiring them.
- Next-generation therapeutics will offer clinical benefits; however, high list prices, small patient populations, bioethical questions surrounding gene editing, and limited manufacturing capacities may dampen growth, resulting in only five to eight approvals in the next five years.
- New approaches to—and investment in—treatments for neglected tropical diseases will be sponsored by international organizations and philanthropic organizations.
- A seven-year decline in prescription opioid use in the US will continue, resulting in prescription declines of one-half to one-third the current level measured in 2018.
- Prescription digital therapeutics are a new emerging treatment modality and could be applied in areas where drug therapy alone has left unmet needs, such as behavioral health and cognition. Digital developers may seek partnerships with pharmaceutical companies.

Reference

1. M. Aitken, et. al., *The Global Use of Medicine in 2019 and Outlook to 2023: Forecasts and Areas to Watch*, IQVIA, January 2019. **PT**

Rita Peters is editorial director of *Pharmaceutical Technology*. Send your thoughts and story ideas to rita.peters@ubm.com.

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The Flexicon FPC60 peristaltic fill/finish system from Watson-Marlow Fluid Technology Group can use a variety of modules that allow users to create their own customized filling solution to suit small-batch applications.

The modules include vial infeed, filling, stoppering, capping, auto-reject, gas purging, and product outfeed. The small-footprint system can handle vial sizes between 2R and 100H and has servo-driven auto adjustment, which allows for minimal tools and quicker set-up between batches. When supplied with in-line check weighing, the system offers dynamic prime, no-intervention initial calibration and dynamic recalibration, meaning each vial is confirmed to be within specification.

According to the company, filling is assured from less than 0.2ml up to 100ml. Features include throughput of up to 45 vials per minute, options for automatic segregation of rejects, fluid path developed for single use, horizontally mounted pump head for one-handed interaction, remote operation from outside a cleanroom or distant location, and a SQL server-based data management system. Additionally, the integration of laminar airflow, restricted-access barrier systems, or isolators is also available.

Watson-Marlow Fluid Technology Group
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Kimberly-Clark Professional's Kimtech A5 Sterile Boot Covers with Clean-Don Ties and Vinyl Edge provide reliable sterile protection for ISO Class 5 or higher cleanrooms.

The boot covers are made of 100% polypropylene breathable spunbond-meltblown-spunbond fabric and have Clean-Don ties for enhanced protection and a secure fit. A two-inch vinyl edge allows for an improved moisture barrier.

The CE-certified boots are made without natural rubber latex, silicone, or BHT preservatives and are triple-bagged and vacuum-packaged. Each individually bagged pair of boot covers has a visual sterilization indicator to show that it has undergone gamma sterilization. Available sizes include small/medium, large/extra-large, and universal.

Kimberly-Clark Professional
www.KCProfessional.com

Automatic Desiccant Inserter

The Pharmafill PS1 Packserter desiccant inserter from Deitz Company features a proprietary cut length sensor system that automatically verifies the desiccant, oxygen absorber, or other packet has been properly fed from the continuous strip before allowing it to be cut for inserting. The cut length sensor system uses dualfiber optic sensors to constantly check for long feeds and short feeds and automatically stops the machine's operation in the event of a misfeed, flashes the red stack light, and alerts the operator before the cutting mechanism can slice the pouch and spill its contents. When corrected, the system may be quickly restarted via the touch-screen human-machine interface.

The company reports that the stainless-steel inserting machine allows desiccant insertion of one or multiple packets into bottles or other containers at speeds of up to 100 per minute in non-stop, unattended operation. The system operates with a range of packets in varying materials and thicknesses as well as a variety of containers in different shapes and sizes. Other features include programmable logic controls with touch-screen interface and a hinged safety panel for interior access.

Deitz Company
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Multi-Shaft Mixer and Disperser

The Ross VersaMix is a multi-shaft mixer suited for viscous applications requiring a high level of accuracy and batch-to-batch consistency.

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The VMC-200 model has a maximum working capacity of 200 gallons. An air/oil lift raises and lowers the agitators into the vacuum-rated vessel. All product contact surfaces are stainless-steel type 316L polished 180-grit finish. The ASME 60-psi jacket on the vessel is insulated with two-inch thick mineral wool and sheathed with water-tight stainless-steel cladding.

Equipped with a 10HP anchor agitator, 20HP disperser, and 25HP rotor/stator, the mixer delivers a combination of laminar bulk flow and intensity necessary for homogenization and deagglomeration in high-viscosity conditions up to several hundred thousand centipoises. The vacuum cover includes multiple charging ports, viewing windows, tank light, and a thermoprobe. Finished product is discharged out of a three-inch pneumatically-actuated diaphragm valve installed on the tank's conical bottom.

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FDA Promotes Quality Standards to Reduce Shortages

Jill Wechsler

Policies emphasize the importance of ensuring data integrity in the United States and abroad.

With drug shortages on the rise—driving up prices of scarce medicines in the process—and data integrity transgressions increasingly visible in inspection reports, FDA officials are highlighting the importance of strategies for ensuring a reliable supply of critical pharmaceuticals that meet regulatory standards. The agency is issuing new guidance, cracking down on violative products, and emphasizing the need for greater vigilance and innovation to advance quality drug manufacturing.

The recall of hundreds of batches of valsartan blood pressure medicines made with APIs from China containing a suspected carcinogen set off alarms in 2018 about tainted drugs and inadequate quality controls. As the crisis expanded, leading generics makers recalled multiple products, creating shortages and evidently leading to price increases by producers of untainted valsartan-containing therapies able to document quality.

Such failings in pharmaceutical production have prompted FDA Commissioner Scott Gottlieb and other agency officials to highlight the importance of industry efforts to maintain standards. FDA aims to foster "a culture of compliance" where companies follow best practices and requirements of the law not just to avoid liability, but to support a "shared commitment to serve as good stewards of the public health," Gottlieb commented at the December 2018 Enforcement, Litigation and Compliance conference sponsored by the Food and Drug Law Institute (FDLI) (1).

The emphasis on ensuring quality data has become a global issue.

The commissioner highlighted the importance of high-quality data in submissions and manufacturing systems, noting that inaccurate information on manufacturing often masks production problems and failures. At the conference, Gottlieb announced an updated FDA guidance on data integrity and good manufacturing practices (GMPs) to prevent lapses in this area and help firms create "a quality culture" where employees understand the importance of ensuring that accurate information is developed and submitted to the agency (2). While inaccurate data and information may arise from deceptive practices, Gottlieb noted that more often such errors reflect inadequate processes and systems. The new advisory updates a draft from 2016 and provides advice to help manufacturers identify data integrity lapses, implement best practices, and ensure commitment to standards. Data integrity failures are cited in three-fourths of FDA warning letters, a trend that agency officials hope to address in the latest guidance.

The emphasis on ensuring quality data in pharmaceutical operations has become a global issue. The Pharmaceutical Inspection Cooperation Scheme (PIC/S) released a draft guidance outlining recommended GMP inspection practices, with an emphasis on defining and detecting data integrity vulnerabilities and strategies to harmonize inspection practices (3).

Targeting inspections

Donald Ashley, director of the Office of Compliance in FDA's Center for Drug Evaluation and Research (CDER), reported at the FDLI conference a rise in warning letters involving cGMP issues. One factor, Ashley explained, is linking that trend to an increase in inspections of never-visited facilities, particularly firms producing over-the-counter products. FDA has updated its site-selection model to focus inspections on higher-risk facilities, part of the agency's Program Alignment plan that aims to bring greater expertise and consistency to field operations. Warning letters continued to increase in 2018 for firms in India, China, and other nations.

FDA also seeks to improve production methods and standards for sterile injectable products by launching the first New Inspection Protocol Project (NIPP) in this area. A pilot program

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aims to collect data in a structured manner to improve the consistency and efficiency of inspections for these products, with an eye to better detecting and preventing lapses in an area where quality manufacturing issues have led to shortages and closures (4).

In addition to more targeted and efficient inspections, FDA aims to reduce duplicative site visits that waste resources and impose a burden on industry by fully implementing a Mutual Reliance Agreement (MRA) with the European Union. This program allows FDA to rely on information from drug inspections conducted within each other's borders and thus avoid visiting operations that show strong compliance histories. FDA has completed assessments that enable it to recognize the inspection capabilities of 20 EU member states and aims to complete the task by July 2019. The parties also plan to extend the agreement to veterinary medicines this year and to certain vaccines by 2022.

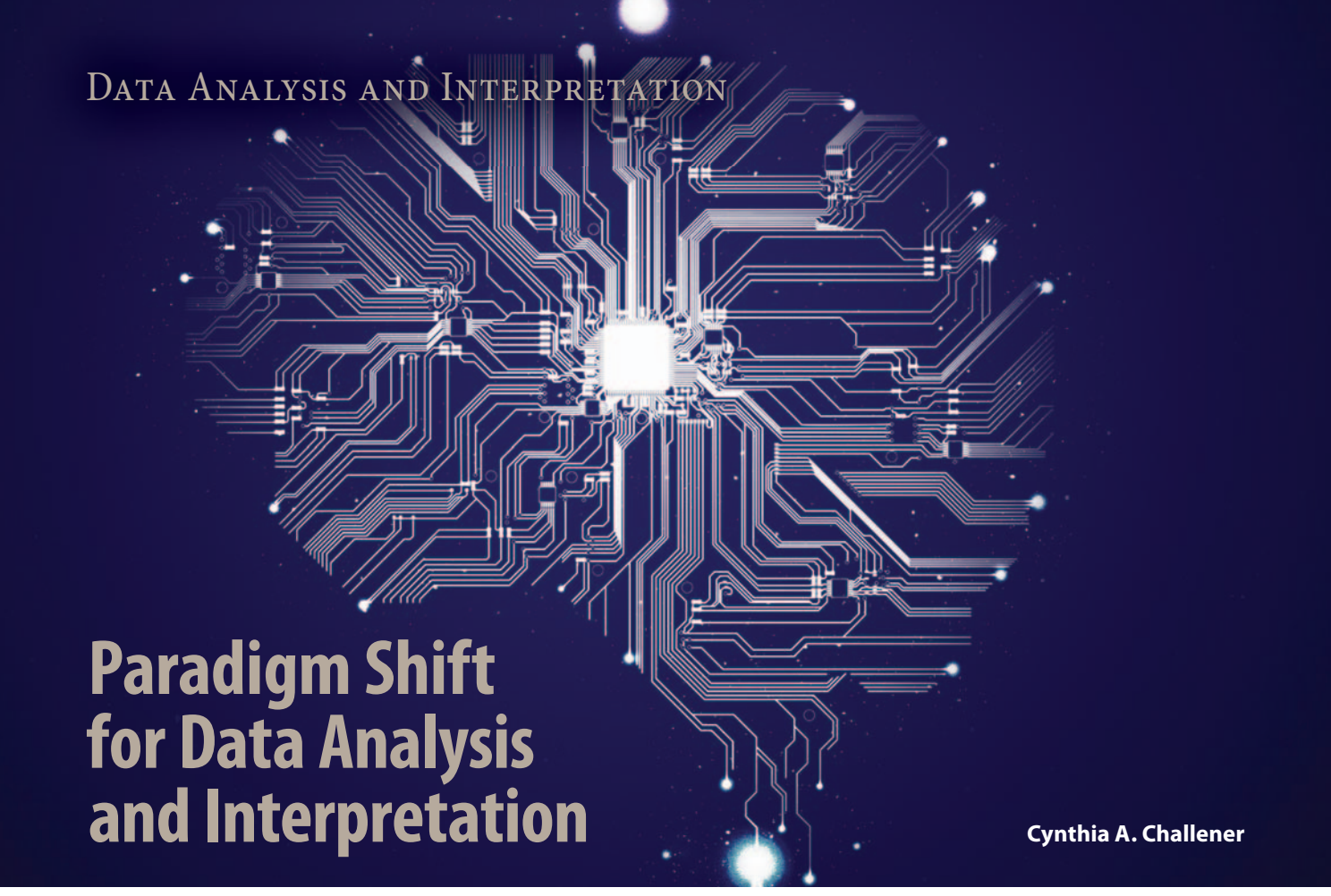
International collaboration also has been extended to GMP inspections of plants producing APIs to similarly avoid duplicative inspections. The program was useful in allowing information sharing regarding planned inspections of valsartan API facilities in order to target oversight to uninspected plants.

Added resources, moreover, have enhanced FDA's ability to expand its capacity to block the import of violative food and medical products. The agency has increased the number of inspectors at international mail facilities and plans to expand the number of packages it can review to better detect dangerous or counterfeit drugs, particularly illegal opioid products.

While FDA wants to assist industry in avoiding regulatory violations, Gottlieb emphasized that the agency will take action when it sees "willful disregard for the rights or even the safety of people" affected by substandard or adulterated products (1). He expressed optimism that these initiatives in FDA's inspection program will better target oversight to products and processes that pose a greater risk to public health.

References

1. FDA, "Remarks by Dr. Gottlieb to the FDLI Enforcement, Litigation, and Compliance Conference," FDA.gov, Dec. 12, 2018.
2. FDA, *Data Integrity and Compliance with Drug CGMP, Questions and Answers, Guidance for Industry* (CDER, December 2018), www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM495891.pdf
3. PIC/S, *Guidance on Classification of GMP Deficiencies* (PIC/S, January 2019), www.picscheme.org/en/publications?tri=date.
4. FDA, "Statement from FDA Commissioner Scott Gottlieb, M.D., on New Steps to Strengthen and Modernize Agency's Oversight and Reporting of Inspections for Sterile Injectable Drugs," Nov. 9, 2018, www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm625601.htm **PT**



Paradigm Shift for Data Analysis and Interpretation

Cynthia A. Challener

Leveraging vast quantities of analytical data requires digitalization and platform integration.

Analytical instruments are increasing in sensitivity and accuracy. Pharmaceutical methods applied today generate increasing quantities of data. These data are stored and manipulated using a variety of software platforms from different suppliers. Pharmaceutical scientists must be able to integrate and interpret these data in an efficient manner that ensures reliability, security, and regulatory compliance.

Digitalization creates difficulties

Today's modern laboratory is highly dependent on a range of instrumental technologies, all reliant on data output that has to be interpreted, managed, and maintained in a retrievable, secure, and non-corruptible manner, according to Mark Rogers, global technical director at SGS Life Sciences. The volume and complexity of these data make the move to electronic capture inescapable, he adds.

For many of these techniques, however, the inevitable evolution from paper-based data collection procedures to electronic systems has not been without difficulties. "It may be argued, for example, that the relatively simple process of recovering and reviewing chart recordings from a well-maintained paper archive has advantages over the recovery of data from older software/operating platforms that may have become obsolete, making data difficult to retrieve," Rogers explains.

Regulatory considerations have also now become intrinsically linked to the traceability, security, and non-corruptibility of scientific data, again resulting in difficulties with older equipment, he notes. "The electronic modernization of older—but well-established and effective—equipment may be one of the most significant and ongoing challenges," asserts Rogers.

In addition, despite advances in the digitalization of analytical data, significant human intervention and manipulation is still required during any decision-making process based on data acquisition. For lot release, once a specification (identify, purity, physical form, etc.) has been established and test methods validated for a drug substance, there are many human intervention steps involved to get from a request for release to fulfilling that request, explains Andrew Anderson, vice-president of innovation and informatics strategy at ACD/Labs. Spectra must be collected and separation analyses performed. The data obtained must be generated as a table, chart, or other picture that describes the results, which must then be compared to reference standards to determine whether they conform or not.

"Many of these steps cannot be digitized or even easily automated. Bringing data back into the decision-making

Cynthia A. Challener, PhD, is a contributing editor to *Pharmaceutical Technology*.

mechanism is very difficult without specialized informatic tools that handle all different types of data. This challenge is the greatest latent pain for development organizations," Anderson asserts.

Volume and complexity challenges

There will also always be challenges with getting the right data, according to Anderson. "There are trade-offs between project timelines and the data that can possibly be generated and ultimately handled by existing infrastructure," he explains.

One example relates to the move to a quality-by-design approach to process development. With this approach comes a geometric expansion in the quantity of data being acquired to characterize a process. Each possible parameter variant requires a data point for the modeling system used to determine the optimum operating conditions.

In addition, the data itself is becoming more complex. A nuclear magnetic resonance (NMR) spectrum provides a significant amount of detailed information about a given molecule and is therefore attractive for small-molecule API proof-of-structure analysis. Interpretation of this type of spectrum, such as comparison with a reference standard to confirm identity, requires an expert, however. "A method for plant operators to use for determining that a lot spectrum conforms to a standard should be rugged and allow for simple acquisition and validation. Ultraviolet (UV) analysis is one example. Such a method leaves some doubt however; NMR provides more fidelity, so there is a tradeoff between absolute confirmation and practicality," Anderson observes.

The complexity of analytical experiments will, in fact, always outpace the ability to implement them in quality processes, he adds. "There are often challenges to implementing more complex analytical techniques in a quality paradigm. All of the aspects of quality assurance are increasing in complexity: software systems and how they handle data, quality practices, standard operating procedures, and test methods. Each of these factors must be considered to ensure that drug products introduced to the market are of the highest quality," notes Anderson.

It is not only the volume and complexity of raw data being generated that is the key issue for Marco Galesio, R&D team leader in the analytical chemistry development group at Hovione, but the lack of specific and user-friendly software to treat and interpret these data. "Most of the time there is a lot of relevant data being generated, but due to lack of suitable software and sufficient time, it is not possible to take the most out of it," he says.

Challenges bigger for biologics

Biologic drugs pose some additional challenges beyond those associated with chemical APIs. Small molecules have one structure and composition. Because biologic drug substances are produced in cells or microorganisms, their structures and compositions can vary slightly from batch to batch, leading to inherent variability, according to Tiffani A. Manolis, senior director of Agilent Technologies' global pharma strategic program.

Added to this variability is the complexity of large-molecule structures, which necessitates the use of a greater number of more complex analytical methodologies, according to Íñigo Rodríguez-Mendieta, technical client manager biopharmaceuticals, SGS Life Sciences. In most cases, specific expertise is required to interpret large-molecule data, notes Constança Cacela, associate director of R&D in the analytical chemistry development group at Hovione.

The necessity to fully define the relatively complex and diverse structural features of large molecule entities has led to expansion in the variability and sophistication of the analytical tools in the biologics field, according to Rodríguez-Mendieta. "Many of these techniques have traditionally been employed in the academic sector where data interpretation relies heavily on subjective manual review, and this is often difficult to translate to machine-based understanding," he says. Approaches to digitalization have included automated reference to library data as in the case of circular dichroism (CD) and/or the application of complex algorithms as in the case of mass spectrometry (MS)-based sequencing. "None of these approaches has yet been perfected, however, particularly for large-molecule applications where structural diversity can prove a significant impediment to accurate interpretation," adds Rodríguez-Mendieta.

The key challenge lies in the fact that with biologic molecules, identity has various meanings related to structure (primary, secondary, etc.), post-translational modifications (PTMs), etc. "Orthogonal analyses are required to ensure full characterization. Chromatography may be used to determine purity, while other methods must be used to determine the identity (sequence, location of PTMs, etc.). Structural assays are often augmented with behavior immunoassays. All of these data must be 'assembled' together to create the complete picture. That can be challenging to do digitally, because orthogonal data are often generated in a variety of vendor formats," Anderson explains.

The same issues exist for biosimilar comparability studies, Rodríguez-Mendieta notes. "Results have to be considered holistically, which remains a considerable challenge, as the data can be somewhat contradictory and often produced from a wide range of techniques with instrumentation from multiple manufacturers with different data platforms," he says.

Next-generation drug substances can complicate the situation even further. Anderson points to antibody-drug conjugates (ADCs) as an example. "ADCs comprise an antibody, a small-molecule cytotoxic payload, and a linker of some kind, which can be an oligomer or other small to medium-sized component. The dynamic range of MS, NMR, or other instruments must therefore be sufficiently wide to allow analysis of small and large molecules, and of course also validatable," he explains.

Difficulties magnified in MS and NMR

Separation techniques such as gas chromatography (GC), high-performance liquid chromatography (HPLC), capillary electrophoresis (CE), and gel elec-

trophoresis when coupled to UV, Raman, infrared, and fluorescence do not provide sufficient data per se, and particularly for large molecules, according to Cacela. "Data generated by these techniques must often be validated by more comprehensive techniques such as mass spectrometry," she notes.

In general, however, LC–MS methods, especially high-resolution MS (quadrupole time-of-flight [Q-TOF], triple quadrupole, etc.), generate overwhelmingly large data files, according to Manolis. "Data sets are becoming very large and pose challenges to any IT [information technology] infrastructure as they are transmitted across networks for storing and analysis," she observes.

An additional challenge is related to data interpretation. The acquisition of MS data occurs in much less time than it takes to interpret it, according to Anderson. "With TOF instruments it is possible to gather detailed spectra in just three minutes, so the technique can be useful for screening experiments or monitoring the progress of a synthetic reaction or cell culture. The data files that result can be a gigabyte in size, which is challenging not only from a hard disc perspective, but for interpretation, which can take much longer," he comments. Furthermore, deep expertise is required to accurately evaluate and filter the meaningful data, Cacela adds.

Similarly, the volume of data generated in NMR and surface plasmon resonance analyses can be challenging to manage.

Issues with data abstraction

Another challenge given the volume and complexity of data generated today is the need for some sort of data abstraction in order to be able to efficiently leverage analytical data in the decision-making process. "Very large data sets need to be transformed in some way to make them manageable and interpretable in a practical and timely manner. The difficulty, however, is the potential for loss of information," asserts Anderson.

Reduction of data creates risk from a total analysis point of view, he adds. Centroided MS data vs. full-profile MS data is one example. The former involves a mathematical transformation of the data that provides simplification and easier interpretation, but the risk of missing important details must be weighed against that simplification.

There is a big push, according to Anderson, to find ways to use data in a non-reduced way for more practical interpretations. One example involves modifying the way signals are acquired. In NMR, for instance, Anderson points to nonuniform sampling, which involves pulsing the sample at nonuniform frequencies and allows the reconstruction of spectra close to what would be obtained with full-frequency pulsing but in a smaller data file.

There is also a focus on the application of machine learning and artificial intelligence in this area, letting machines identify trends and make observations that humans could probably find but don't have time to do, according to Anderson.

Need for a multi-modal view

A theme underlying all of the above areas of concern is the need for software platforms that enable viewing of data generated by different instruments from different suppliers. "The systems we have today generate huge amounts of data. But these same systems are not necessarily capable of integrating these large data sets and providing researchers with actionable information in a multi-modal view," Manolis states. While data generation and usability of technologies are improving with better user interfaces and easier-to-use systems and applications, the integration of data sets and connectivity between data sets from different technologies and vendors remains a challenge.

"Software analysis tools, rather than only gather data, should also be able to analyze and interpret that data and provide information as the output," asserts Lucia Sousa, associate analytical chemist for R&D in the analytical chemistry development group at Hovione. "Vendors are creating software that interprets data, but even these advanced systems still require great effort from the user. Scientists in the laboratory should have knowledge in their fields of expertise and not need to be experts in software applications as well," she adds.

Throughout pharma discovery, development, and commercial manufacturing, data are acquired and stored on separate and disparate systems that contain both structured and unstructured information, according to Manolis. The challenge is further complicated by collaboration with outsourcing partners, suppliers, distributors, and government agencies that have their own disparate systems. Overcoming these challenges will dramatically improve researchers' abilities to make faster decisions and will ultimately accelerate drug development and approval, she adds.

Analytical manufacturers are working with pharma companies and others to build software solutions that ease these processes. The Agilent data system OpenLab CDS ChemStation Edition, according to Manolis, is the first to support the new Allotrope Data Format (ADF) (allotrope.org), an emerging standard developed by a consortium of pharmaceutical companies.

"ADF standardizes the collection, exchange, and storage of analytical data captured in laboratory workflows and enables labs to transfer and share that data across platforms," Manolis explains. "There needs to be continued focus on evolving customer requirements concerning analysis and integration of data sets, compliant solutions for analysis and storage, and the IT infrastructure challenges around large data sets, specifically those generated from high-resolution MS analyses," she continues.

It is an exciting time with respect to advances in data analysis and interpretation, according to Anderson. "Instrument manufacturers and software vendors like ACD/Labs are facing a new paradigm. No longer are we dealing with the integration of monolithic systems through document exchange. Copying and pasting spectra into a word document isn't good enough any longer. Integration of not only data, but applications is needed to provide a seamless user experience. Decision-making interfaces of the future will be interoperable and able to leverage a variety of heterogeneous and orthogonal data," he explains.

contin. on page 47

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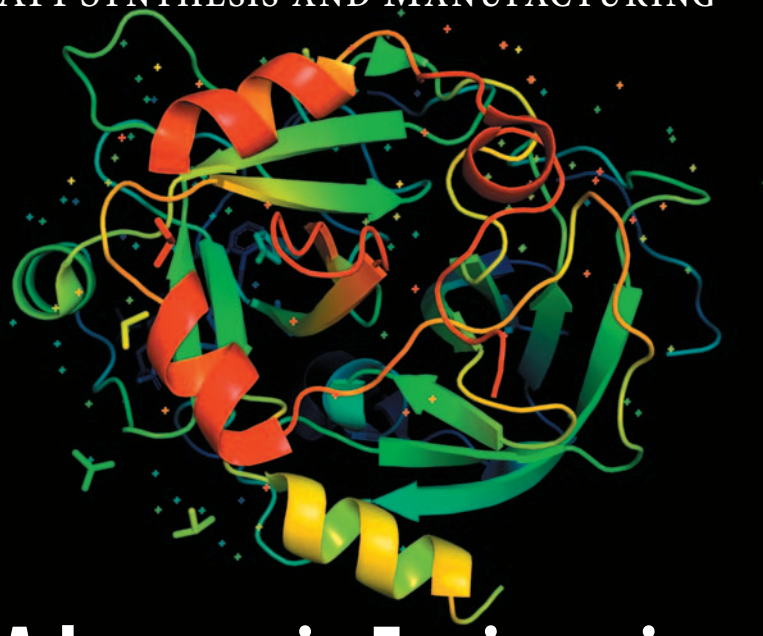

Advances in Engineering of Protein-Based APIs

Cynthia A. Challener

New platform technologies, advanced modeling tools, and addressing patient needs are important developments.

Engineering of protein therapeutics has advanced significantly since the first biologic drugs were introduced. Today, monoclonal antibodies (mAbs) have become one of the predominant forms of protein-based biopharmaceuticals, with humanization and fully human monoclonals contributing to their increasing success. Antibody-drug conjugates are a second-generation version leveraging the attributes of both small and large molecules. Bi/multispecific and fusion proteins are emerging as promising third-generation protein drug substances. Peptides and peptidomimetic therapeutics offer the advantages of mAbs but in smaller molecules that may be formulated for oral delivery. Advanced modeling tools are enabling the rapid engineering of more complex proteins with desirable properties. Companies are also paying close attention to the developability and manufacturability of proteins and considering patient needs at the earliest engineering stages, leading to safer and more effective biologic drugs.

Cynthia A. Challener, PhD is a contributing editor to *Pharmaceutical Technology*.

Fully human monoclonals and mAb humanization

Fully human mAb therapeutics with fully human sequences have reduced immunogenicity potential and improved safety and efficacy, enabling chronic treatment without liabilities, according to Jennitte Stevens, director of process development at Amgen. Generation of fully human antibodies is achieved in transgenic animals. For instance, mouse cells that produce mAbs have been modified by knocking in human genes and knocking out mouse genes. Amgen's XenoMouse technology has been used to produce the marketed mAb therapeutics denosumab, erenumab, and evolocumab.

Recently, more fully human platform technologies have been developed, such as OmniAb (Ligand), Trianni Mouse (Trianni), and huTARG (Innovative Targeting Solutions). "The latter is a fully mammalian technology that generates *in-vitro* antibody diversity through e*x-vivo* V(D)J recombination in cultured cells. These technologies enhance both the speed and success of developing antibody therapeutics," Stevens says.

Humanization of mAbs is another well-established method to generate therapeutic antibodies when transgenic technology is not available or feasible, according to Stevens. "Humanization techniques using complementary determining regions grafting or phage display have enabled the advancement of numerous antibody therapeutics (such as trastuzumab, pembrolizumab, and romosozumab) to the clinic and ultimately to patients. Humanized antibodies may also have improved safety and immunogenicity profiles, which is a desirable outcome for patients," she observes.

Bi/multispecific proteins

Bispecific antibodies are an important emerging area in advancing protein engineering for pharmaceutical products, and several bispecifics based on immunoglobulin scaffolds are currently in clinical development, according to Mark Smythe, founder and currently vice-president of technology for Protagonist Therapeutics.

"Protein therapeutics traditionally were designed as single receptor/protein antagonists or agonists. But to effectively combat disease, many future drugs will require multiple proteins being agonized or antagonized to achieve efficacy, namely in the immune-oncology and inflammation space," Stevens explains.

One example is bispecific T-cell engagers (BiTEs). Blincyto, a BiTE targeting CD3 and CD19, became the first bispecific biologic approved in the US

market and demonstrates the impact bispecific molecules can have on treatment of disease, according to Stevens.

"Ongoing IgG-based modular domain engineering and platform development in multispecifics present great potential to elicit synergistic activities, enhanced therapeutic index (efficacy, selectivity, novel signaling) or safety, effector cell retargeting, half-life extension and/or as a trojan horse as well as improved convenience, all of which can result in significantly improved outcomes for patients," Stevens asserts.

One example comes from Alligator Bioscience, a Swedish clinical-stage biotechnology company developing tumor-directed immuno-oncology antibody drugs. In January 2019, the company launched its IgG-like RUBY bispecific antibody format that allows plug-and-play generation of bispecific compounds from any two antibodies. The bispecific antibodies consist of immunoglobulins fused via the C-terminal heavy chains to Fab domains, which are attached via their light chains, allowing for unrestrained dual binding to two targets with a bivalent interaction in a manner similar to the natural antibody-antigen interaction. The result is bispecifics with excellent stability and manufacturability properties, superior binding, and dramatically shortened development timelines, according to the company.

Bispecifics based on non-immunoglobulin scaffolds that overcome some of the limitations of immunoglobulin scaffolds are also being pursued by multiple developers, including Molecular Partners, Ablynx, and Covagen. More than 100 formats of bispecific/multispecific candidates are being engineered across the industry, many in the oncology space, according to Stevens.

Peptides and peptidomimetic therapeutics

Although mAbs have led to the development of many meaningful biotherapeutics and provide the clearest examples of successful protein engineering technology, Smythe notes that they have significant practical limitations in therapeutic use, such as the inability to deliver biologics or peptides by oral administration. "One type of recent advance in peptide engineering has been the design of protein-based therapeutics that can bind the same targets or block the same pathways as clinically validated antibodies, while allowing oral administration. This advance can be seen in drug candidates based on constrained peptides, such as those from Protagonist Therapeutics, and in the formulation design of an oral GLP-1 agonist from Novo Nordisk," he says.

Effector-free mAbs

For therapeutic applications that do not require effector function, engineering of an IgG scaffold lacking effector function can streamline development and commercialization of such a therapeutic, according Stevens. "Various strategies have been developed recently to eliminate Fc-associated effector binding and functions such as antibody-dependent cell-mediated cytotoxicity and complement dependent cytotoxicity activity," she observes. For example, Amgen has developed a stable effector functionless IgG platform to eliminate off-target effects while maintaining the stability and half-life expected of a traditional antibody.

New protein engineering strategies

Advances have not been limited to novel protein formats. New strategies are also being applied to the development of engineered proteins that integrate developability prediction, manufacturability assessment, and quality-by-design early in the process. "This approach is critical to achieving right-first-time outcomes during the development and commercialization cycle of a biologic," asserts Stevens.

Amgen has developed a next-generation antibody engineering strategy that enables reliable and efficient identification of pre-candidate leads from early screening lead molecules. "We translate patient needs into protein design requirements during development and engineer in attributes to meet biological performance and molecule stability, which provide improved delivery for desired patient outcomes and improved processing during manufacturing. Incorporating patient needs into molecule designs starts with a translation of the target product profile into a quality target product profile followed by application of these targets during selection and engineering of molecules. This process enables faster and more efficient advancement of novel and effective therapies to patients while improving the overall patient experience," Stevens explains.

Modeling tools and more

A combination of structure-based drug design with library approaches has become a powerful tool in protein engineering, according to Stevens. "Merging these approaches enables a focused library design that can yield desired protein characteristics rapidly by eliminating the repeated rounds of screening required in a random library approach. At the same time, it enables exploration of a much wider design space than is possible using pure rational design approaches," she notes.

More advances can be expected, too. Continued improvements in *in-silico* approaches (modeling, software, and especially machine learning and artificial intelligence) for the prediction of critical molecule attributes such as aggregation, viscosity, and immunogenicity from primary sequences will significantly increase the success rate, accelerate molecule advancement, and reduce the overall resources required to advance a molecule from the discovery to the clinic, according to Stevens.

Similarly, miniaturization and high-throughput versions of protein assays will reduce analysis times and enable exploration of wider design spaces. Stevens points to nanofluidic characterization assays for antibody identification and developability assessments as one example.

Cell-free protein synthesis is also promising, but at this point is limited by the current capabilities in gene synthesis, which serves as a bottleneck for throughput. "Low cost, rapid, and precise gene synthesis will be hugely enabling in this area," says Stevens. **PT**

A User-Friendly Approach to Developing an Extended-Release Product

Martin Koeberle

The challenge of achieving sustained delivery of an active ingredient or nutrient can be achieved with extended-release formulations.

To effectively treat many conditions, it is beneficial for the API or nutrient to be slowly released from the dosage form over a prolonged period of time. Take the treatment of magnesium deficiency, for example. Magnesium is an essential mineral that is important for many vital functions. Magnesium deficiency has been linked to a range of conditions, including diabetes, metabolic syndrome, and coronary artery disease (1). Despite its importance, many individuals do not receive sufficient amounts in their diet. Certain populations, such as athletes and pregnant women, also have an increased need. As a result, supplements are taken to boost magnesium levels.

To be most effective, dosing of this important nutrient should be intelligently managed. The body is able to absorb more magnesium when it is supplied as a steady stream rather than as a large single burst. Any excess magnesium that is taken but not absorbed is simply excreted from the body. One approach to dosing a regular supply of magnesium is to take multiple, immediate-release dosage forms at regular intervals throughout the day. This can be inconvenient, however, and lead to poor compliance to dosing routines. With individuals increasingly expecting convenience in all areas of their lives, the requirement to carry with them and remember to take multiple doses of a nutraceutical product simply does not meet their needs.

So how can sustained delivery of an active ingredient or nutrient be achieved over extended periods of time, while ensuring products are user-friendly?

Development challenge

For many developers, the solution to this challenge is extended-release formulations that steadily deliver the active ingredient or nutrient to the body over a certain period of time. A single dose of an extended-release formulation can successfully achieve sustained blood plasma concentrations at levels that would otherwise require multiple immediate-release doses.

There are a number of options available when developing extended-release formulations. One fundamental way of prolonging the release profile of a product is through chemical modification of the API using a poorly soluble salt. This approach is essentially counter to the traditional strategy of improving the bioavailability characteristics of a pharmaceutical or nutraceutical product by selecting a highly soluble ion pair combination. Another relatively straightforward approach is to decrease the rate of dissolution by reducing the surface area of the API. This can be achieved by using large crystals instead of small or micronized particles. While these approaches can be effective for some products, for longer-release profiles, more sophisticated technologies are required.

An alternative means of controlling the release of APIs or nutrients where more extended-release profiles are required is the use of various formulation strategies. One of the common approaches is the use of matrix systems, which involve mixing and compressing the API or nutraceutical ingredient with a gelling or swelling excipient that slows the rate of dissolution. Various matrices can be used, including hydrophilic or hydrophobic polymers or lipid excipients.

Another strategy for developing extended-release products is the use of osmotic pump formulations. These take the form of a tablet or capsule consisting of an API-containing core sur-

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rounded by a semi-permeable membrane into which one or more holes have been laser-drilled. As the formulation absorbs water and swells, the API is slowly forced out of the hole by osmotic pressure. While these dosage forms are more tolerant of variations in gastrointestinal conditions and are capable of delivering very consistent results, they are often cost-prohibitive to use for most over-the-counter products, such as nutraceuticals.

An effective and more affordable approach for developing extended-release products is the use of coating technologies.

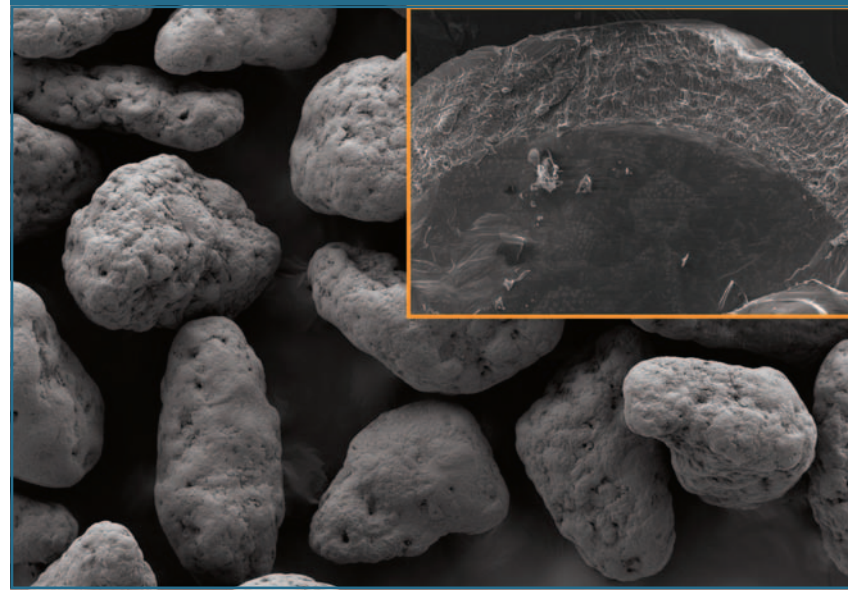
Coating technologies

An effective and more affordable approach for developing extended-release products is the use of coating technologies. Through the careful selection of appropriate coating agents, the rate of dissolution of the nutrient can be controlled, facilitating immediate, extended, or even delayed release depending on the requirements of the product.

The traditional coating approach involves using a solution of the API and excipients to coat a seed particle using a fluid bed process. However, a major limitation is the fact that coated particles must be dried, requiring large amounts of time and heat, particularly when the solvent is water. Additionally, multiple coating layers must typically be applied, adding time and cost to manufacturing cycles. As a result, alternative coating technologies have been developed.

Hot melt coating (HMC) is an alternative technology that is better suited to the manufacture of extended-release formulations. HMC involves coating particles of the API or nutrient with a layer of lipid excipient (see **Figure 1**). During manufacture, the seed particles are suspended in a fluid bed coater, while molten excipients are sprayed onto them using a heated nozzle. As the seed particles are maintained at a lower temperature than the melting point of the excipient mix, the molten droplets wet the particles and solidify upon contact, resulting in a homogeneous coating layer.

Figure 1: Scanning electron microscope image of particles coated with a mixture of lipids using hot melt coating (insert: enlargement of a cross-sectioned particle).



Because no solvent is involved, the process is rapid, typically taking less than two hours for commercial batch sizes. Furthermore, once process parameters have been optimized, no curing or sintering effects are typically encountered, and undesirable side effects, such as agglomeration, are greatly minimized. Through the addition of appropriate emulsifiers to the excipient mix, the rate of dissolution can be adjusted to meet the product's requirements.

HMC is applicable to a wide range of oral dosage forms, including multi-layer tablets, multiple unit pellet systems, and hard gelatin capsules. However, when used to create extended-release products, these formulations can be problematic. As extended-release formulations usually have a higher dosage than immediate release products, traditional tablets and capsules must often take a larger form, which can present swallowing difficulties for many people. To overcome this, many individuals resort to crushing, dissolving, or chewing their tablets (and some do not take them at all) (2). These approaches can break down the extended-release mechanism and result in the delivery of a single large dose, with potentially dangerous health consequences.

HMC can be used to manufacture orally disintegrating granules (ODGs), however—a dosage form that overcomes many of the challenges associated with conventional tablets and capsules. ODGs are ideal for extended-release products as they allow a large dose of up to 3000 mg to be delivered in the form of small particles in a single "stick pack". ODGs are poured directly into the mouth and can be easily swallowed without the addition of water. Moreover, as the same coated particles can be used to formulate different finished products (such as those with different dosages or flavors), the combination of HMC and ODGs offers

contin. on page 26

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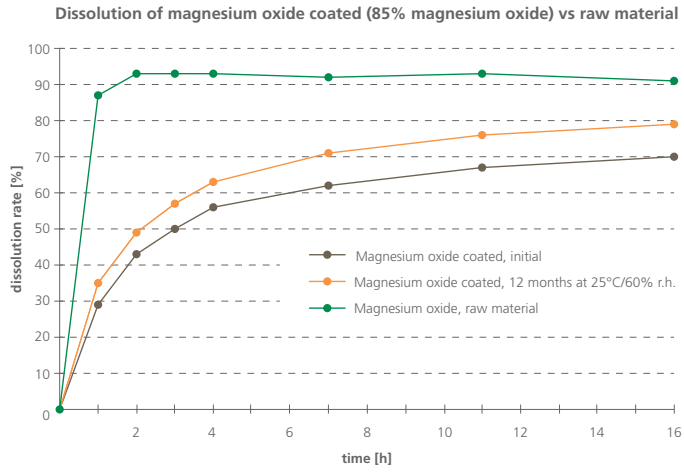
contin. from page 23

Figure 2: Release profiles comparing coated magnesium oxide (85% magnesium oxide) with the raw material. The release profile of the coated product stored for 12 months at 25 °C and 60% relative humidity is also shown. Hot melt coating was used to create the extended release characteristics. Dissolution testing was performed using the USP II (paddle) apparatus at 75 rpm and in 900 mL 0.1 M hydrochloric acid at 37 °C.



manufacturers a cost-effective way of producing a broad product range.

Hot melt coating

Controlling the rate of release of the nutrient and ensuring that product met the expectations of modern consumers were important factors to address when developing a magnesium formulation on behalf of a customer. After considering the options, ODGs manufactured using HMC offered the ideal solution. This combination ensured extended-release of magnesium, while the dosage form could be swallowed easily and had a pleasant taste and mouthfeel.

Figure 2 compares the release profile of the extended-release formulation containing 85% magnesium oxide against the uncoated raw material. The raw material completely dissolved within two hours, whereas the coated material only released approximately 45% of the nutrient over the same time period. Even after 16 hours, just 70% of the nutrient was released, demonstrating the formulation's ability to release magnesium oxide over a prolonged period. These extended-release characteristics could be adjusted by simply varying the amount of coating or by using different coating materials.

The stability of the product was also an important design factor. **Figure 2** shows the release profile of the product stored for a period of 12 months at 25 °C and 60% relative humidity. The dissolution profile of this product was very similar to that measured at the initial time point, indicating the stability of the formulation. Importantly, the extended-release profile was maintained, indicating that long-term storage (climatic zone 2) conditions did not affect the product's ability to deliver magnesium over a sustained period.

Conclusion

Pharmaceutical and nutraceutical companies are often faced with the task of developing dosage forms that produce an effective blood plasma concentration of the (active) ingredient over a prolonged period of time, while delivering a convenient and user-friendly experience for consumers. Extended-release formulations based on the use of orally disintegrating granules and hot melt coating can be an effective solution to this development challenge.

This approach allows developers to tune the release profile to meet the needs of the product, and offers a cost-effective means of establishing a broad product range comprising multiple dosages and flavors. By overcoming the swallowing challenges associated with large dosage forms and offering enhanced taste and mouthfeel, these user-friendly extended-release formulations can help to deliver the pleasant oral experience that modern consumers have come to expect.

References

1. M. Shechter, et al., *Magnes Res* 25 (1) 28–39 (2012).
2. Hermes Pharma, "A Hard Truth to Swallow?" www.swallowingtablets.com, accessed Jul. 25, 2018. **PT**

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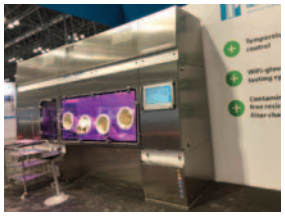

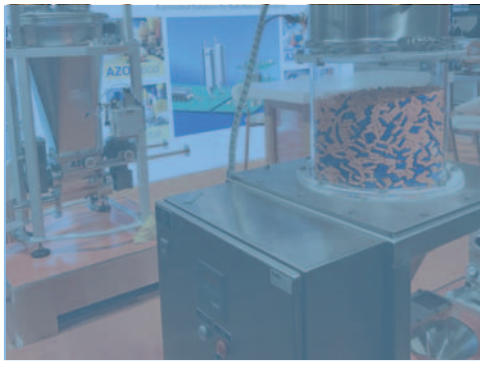

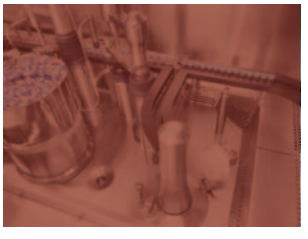

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Process Development Best Practices for Topical Drug Products

Christopher Harrison, Sarah Pratt, and Marc Brown

A QbD approach enables development of a robust control strategy for manufacturing.

Scaling up the manufacture of a topical drug formulation to supply toxicology, clinical, and commercial batches requires a well thought-out strategy. Process development requires modest investment in time and money compared to the risk of batch failure and the consequent adverse effects on timings, costs, and project success. Furthermore, it is not only development programs for new chemical entities (NCEs) that can benefit from process development. It is a step that generic-drug companies omit at their peril, because originator products may not be based on optimized formulations and the correct process parameters needed for their manufacture may not be well defined.

Christopher Harrison is head of Process Development and Manufacture; **Sarah Pratt** is chief operating officer; and **Marc Brown, PhD,** is chief scientific officer and co-founder, all at MedPharm.

A quality-by-design (QbD) approach, in combination with six sigma tools, provides a methodology from which a robust processing control strategy can be derived. The QbD strategy, given the appropriate scale-up considerations, lives with a product throughout its entire life, not just for the initial scale-up for toxicology or clinical batches but also when moving to commercial scale and future plant-to-plant transfers. The benefits of this approach are multiple. Above all, the building-in of quality as opposed to the determination of quality by testing clearly demonstrates to regulatory authorities that control over consistent manufacturing has been established. This increased level of assurance in manufacture reinforces the commercial viability of the product. In addition to experimental design to challenge critical process parameters (CPP), six sigma tools such as failure mode effect analysis (FMEA), input-output diagram, voice of the customer, benchmarking, and evaluation criteria add to the power of the QbD approach.

Applying QbD to topical formulations

Defining a control strategy around CPPs and critical material attributes (CMAs) is of particular importance with semi-solid products. The composition of such products is carefully derived by taking in every aspect of the target product profile while acknowledging the scientific and technical constraints imposed by the API, excipients alone, and in combination. The attributes of each material used can have a profound impact on the resultant formulation in terms of both safety and efficacy, but they can also dictate or heavily influence the manufacturing process especially in areas such as dissolution, mixing parameters, and heating or cooling processes. The safety and efficacy of topical pharmaceutical formulations, such as creams, gels, foams, and ointments, are clearly intimately related to the composition of the product; however, there is often a lack of appreciation for the relationship between clinical performance and the microstructure of the formulation, which is highly dependent upon manufacturing process parameters.

Any process development program aimed at product optimization must, therefore, take into account a broad range of processing parameters to ensure consistent manufacture of pharmaceutical product to the chosen specification. Creams tend to be one of the more complex topical pharmaceutical formulations (1), in which the combining of two immiscible phases requires a defined order and speed of addition of materials; defined speeds and times for the mixing and homogenization steps; and more often than not, a controlled heating and cooling rate during the process (2). The more complex the processing requirements, the more it is likely that the CPP will have an influence upon the control strategy and complexity of the scale-up program.

Generating CQAs

A key tool from the start of any pharmaceutical development program is the

quality target product profile (QTPP). The QTPP ensures that the broad objectives of the project are captured, including the patient and prescriber requirements and the attributes needed to ensure a safe, effective, and commercially viable treatment. The QTPP should always be referred back to when determining the impact of material attributes and process parameters on product quality. From the QTPP, the critical quality attributes (CQAs) of the product may be determined together with an estimation of the impact on product quality of individual raw material attributes and processing parameters (3). Benchmarking against competitor products, especially in the generic-drug market, is a useful guide to the QTPP where it can highlight key commercially relevant differentiators for the new product.

Voice of the customer (VOC) is a six-sigma tool to aid the compilation of the QTPP. It allows the end user and the company sponsoring the development to provide clarity on what they need and want, or do not want in some cases. For a topical pharmaceutical product, the patient voice is paramount, and for orphan products, this is often efficiently captured through internet-connected patient groups. Other significant "voices" are the prescribers and investors. Simple surveys of patients or key opinion leaders (KOLs) are a highly effective means of acquiring valuable VOC data. VOC and the QTPP play a crucial role in the determination of CQAs.

Incorporating risk management

An important element of any efficient process development program is the identification and mitigation of risks. It is widely recognized that the deployment of FMEA as a risk management tool, alongside an appropriate design of experiments, lead to control strategies that reliably produce drug products of the appropriate quality, whether they be based on NCEs or generic drugs. FMEA is a step-by-step approach for estimating the potential risk arising from all possible failures in the design or processing of the topical product. It also highlights where efforts should be deployed in risk mitigation—often defining the most suitable process controls. Many liquid and semi-solid topical pharmaceutical products are, by design or necessity, highly complex systems, often involving multiple phases (e.g., oil and water emulsions) with a defined range of droplet sizes. As such failures can arise in a number of different processing areas, including heterogeneity of drug content, or consistency and physical, chemical, or microbial instability. The efficacy, uniformity of dose, and safety of topical pharmaceuticals rely upon these formulations being homogenous, stable, safe, and easy to use.

Table I: Input–process–output (IPO) diagram showing the unit operations of a sample manufacturing process.

Input	Process	Output
Excipient A, Excipient B, Excipient C	Mixing	Excipient C dissolved, Homogenous solution (1)
Solution (1), Excipient 4, and water	Mixing	Homogenous solution (2)
Excipient 5, Excipient 6, and Excipient 7	Heating, mixing	Clear melt at 65 °C, Homogenous solution (A)
API added to solution (2)	Mixing	API dissolved, Homogenous solution (3)
Homogenous solution (3)	Heating	Mixture at 65 °C, Homogenous solution (B)
Homogenous solution (A) Homogenous solution (B) Excipient 8	Homogenization	Combined solutions
Combined solutions	Stirring, cooling	Final product

Focusing in on the CPPs

The CPPs are derived by establishing the relationship between the processing parameters, the CMAs of both the API and excipients, and the CQAs of the product. A concise way of expressing the process parameters is the six-sigma input–process–output (IPO) diagram (see example in **Table I**). The IPO diagram highlights unit operations and which operational parameters should be investigated in an example manufacturing process.

The first experimental design (DoE), in the form of screening study, is then derived from the outputs of the FMEA (see example in **Table II**) and the IPO diagram. The objective of this pre-screen is to confirm the output from the FMEA, uncover any interactions between key parameters, and to determine processing parameters that are truly critical. Both the experience and expertise of the technical project team and efficient experimental design software are crucial for this approach. Pramod et al. noted that "though design of experiments is not a substitute for experience, expertise, or intelligence, it is a valuable tool for choosing experiments efficiently and systematically to give reliable and coherent information" (4). The FMEA allows the operator to capture the knowledge and decide which areas of the process are most critical and require experimental investigation; the DoE will then validate this thinking statistically and quantitatively.

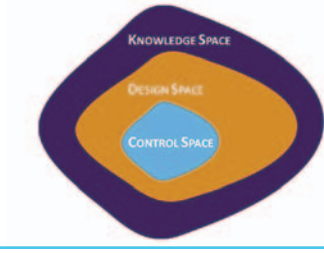
Designing experiments

A crucial factor in the pre-screen and full experiment design for topical formulations is that experiments are conducted using equipment that is representative of larger-scale equipment in order to derive meaningful qualitative CPP data. At MedPharm, IKA LR1000 lab reactors are used, which allow for the control of all typical processing parameters. This approach is crucial to avoid generating "noise" and ensure the quality of the output and the robustness of the resultant control strategy. The understanding of the influence of scale on the CPP from high-quality experimental work con-

Table II: The failure mode effect analysis (FMEA) is used to highlight unit process operations that pose the most risk to product quality. IVRT is *in-vitro* release testing.

Process/ step input	Potential failure mode	Potential failure effects on critical quality attributes	Potential causes	Detection mode	Severity	Probability	Detectability	Total	Current controls	Potential controls
Dispersion of carbopol in water	Incomplete dispersion	Viscosity, content uniformity, visual appearance, homogeneity	Addition too fast, inadequate mixing	Visual, rheology, assay	4	4	1	16	Show addition into a vortex to allow dispersion. Visual check to ensure dispersed.	Use of educator during carbopol addition
	Too much shear applied	Viscosity, API release, content uniformity	Too much shear applied to formulation	Rheology, assay, IVRT	4	4	3	48		Keep speed and/or time of homogenization to a minimum. Avoid homogenisation if possible.
Glycerol and propylene glycol mixing	Incomplere mixing	None	Inadequate mixing	Visual in-progress check	1	1	3	3	Visual check during manufacture to ensure homogenous.	

Figure 1: A graphical representation of the relationship between knowledge space, design space, and control space.



ducted on small-scale forms the basis of any future scale-up work and technical-transfer activities.

For a complex cream, typically 12 experiments should be targeted to cover two to four CPPs in a pre-screening study in preparation for the manufacture of toxicity or clinical batches. The actual number of experiments may have to be expanded depending on the outputs and the associated risks.

Another important factor is that experimental design in both the pre-screen and full study should attempt to push the product to failure to allow for the understanding of the design and control space boundaries. If the developer is conservative in experimentation, they can misunderstand the boundaries between success and failure, and the design space is limited to knowledge space (see **Figure 1**).

A third factor is the identification of what six sigma calls the key process output variable(s) (KPOV), the variables that determine success, and using evaluation criteria to establish whether the method employed to measure the KPOV will detect critical failure. If the answer is no, a mitigation plan is needed. The output of any experimental work will only be as good as the analytical method allows. Topical pharmaceutical products require an array of analytical techniques to evaluate their quality ranging from the commonplace, such as high-performance liquid chromatography (HPLC) and viscosity testing, to more sophisticated methodology, such as rheological evaluation, accelerated stressing to show the potential for separation (5), and *in-vitro* release testing to check that there is no change in the release/thermodynamic activity of the drug from the formulation.

The design space is defined as the multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality (6). It is the boundary of the process parameters to which a product can be made and satisfies the QTPP and CQAs for the product. It is important to stress that there is not a hard border (7) with the knowledge space and that defined process inputs are as important as the measured output. Interpretation of the DoE should point to CPPs and any key interactions between these parameters. Analysis of variants (ANOVA) plots, which show both the mean and the distribution of date around each mean, are particularly useful in this respect as they will clearly show the significance of a parameter or interaction and associated variability. Many experimental design software packages can identify statistically significant effects across a range of parameters and present them in a concise graphic that decision makers find easy to understand.

An important point is that any process change made within the design space is not considered a regulatory change (8),

FIGURE IS COURTESY OF THE AUTHORS.

and hence, has a direct bearing on the flexibility of any future manufacturing process. The more that is known about the boundaries of success and failure, the better the control strategy will be and the less impact that changes in excipient suppliers and specifications will have upon a product over its lifetime.

Ensuring a robust process

The control space represents a range of critical parameters within which the process will yield an assured output to meet the CQAs and target specification at all times. Getting from the design space to the control space can be achieved through the further use of experimental design; typically, two to five factors in full, or fractional factorial, or other surface response design informed by the data from previous experiment design work. A useful guide to DoE can be found online in the form of the engineering statistics handbook (8).

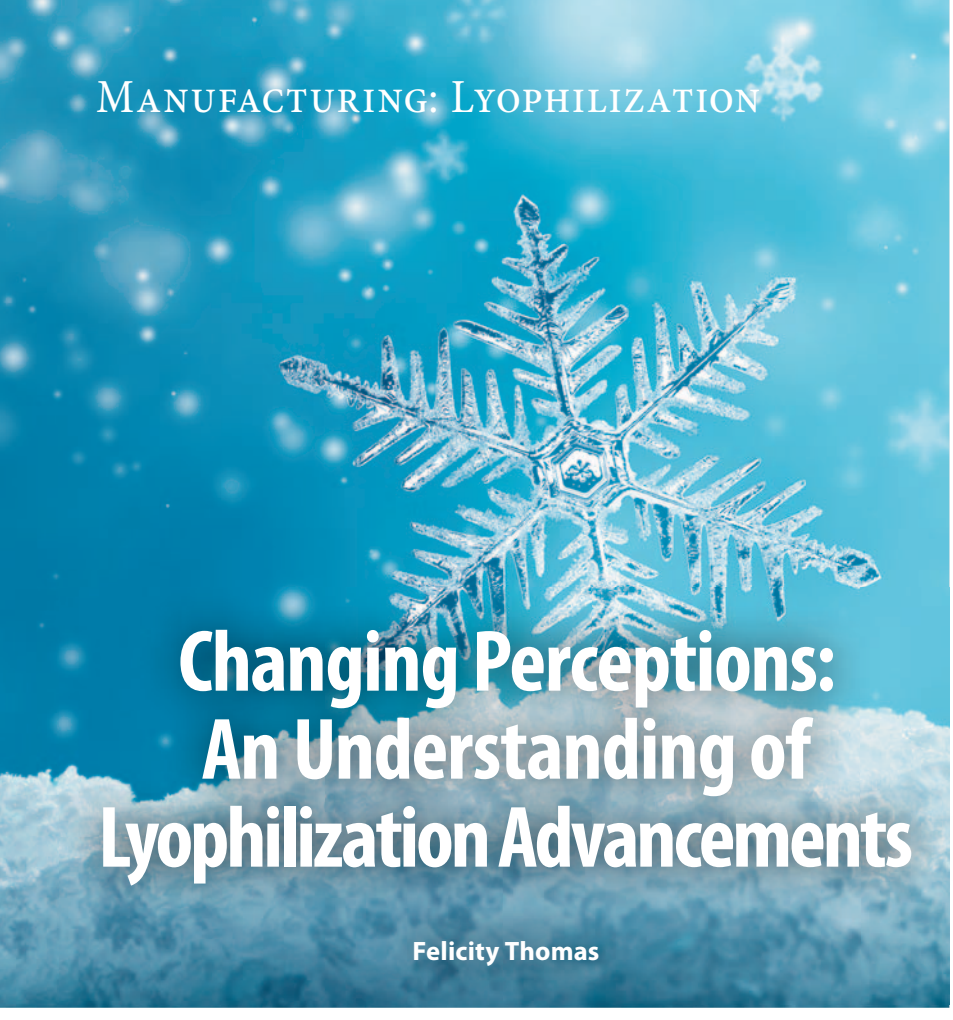
Clearly, the control space for the CPP must sit well within the design space and sufficiently away from the edge of failure to ensure robustness. The interpretation and conclusions from an optimization design will show "best" settings to achieve a product that meets the QTPP and CQAs. A confirmation batch using the optimal settings will demonstrate that the response values from the DoE are close to their predicted values.

Conclusion

Using a stepwise and methodical QbD approach during the development and late-stage formulation of topical products provides a sound and robust platform in establishing the design space for process development and will ultimately enable the developer to provide a robust control strategy for manufacturing. Missing this step can lead to poor processing and physical instability in topical products, which directly impacts product performance and the patients who need the products. The often complex liquid and semi-solid processing for topical products cannot be underestimated, and the marriage of experience, QbD, six-sigma tools, and experimental design ensure that the manufacturing scale-up of complex topical products can be conducted with minimum risk.

References

1. M.E. Aulton and K.M. Taylor, *Pharmaceutics: The Design and Manufacture of Medicines* (Churchill Livingstone Elsevier, Amsterdam, Netherlands, 4th ed., 2013) p. 449.
2. M. Lowenborg, *Pharm. Tech.* 36 (11) (2012).
3. R.K. Chang et al., *AAPS J.* 15 (3) 674–683 (2013).
4. K. Pramod et al., *Int. J. Pharm. Investig.* 6 (3) 129–138 (2016).
5. D. Lerche and T. Sobisch, *J. Dispersion Sci. and Tech.* 32, 1799-1822 (2011).
6. ICH, Q8 (R2) *Pharmaceutical Development*, Step 4 (August 2009).
7. M. Adams, GSK, "Quality by Design & Design for Six Sigma ISPE Breakfast Seminar Toronto," (May 2009).
8. NIST/SEMATECH, NIST/SEMATECH e-Handbook of Statistical Methods, www.nist.gov/programs-projects/nistsematech-engineering-statistics-handbook, accessed July 12, 2018. **PT**



Changing Perceptions: An Understanding of Lyophilization Advancements

Felicity Thomas

Technical advances in process understanding and control must be accompanied by a change in mindset.

Since its introduction to the pharmaceutical industry in the 1940s, lyophilization (freeze-drying) has been a mainstay for manufacturers to stabilize products and ensure they are durable and safe for as long as possible. In recent times, lyophilization has experienced a surge in interest, which has been attributed to the rising proportion of biopharmaceuticals being developed and manufactured that are generally unstable in aqueous form (1).

A stabilizing process

Essentially, lyophilization is the ability to remove water while maintaining chemical or biological function, explains T.N. Thompson, president, Millrock Technology. "It is a three-step process involving freezing, primary drying or sublimation, and secondary drying (sometimes referred to as desorption)," he continues. "Freezing is the most important step of the entire process. If the product is not frozen properly, then the primary drying process can be inefficient or impossible."

"Ultimately, lyophilization is a stabilizing process that is used to preserve the long-term safety, strength, and quality of pharmaceutical products, especially for parenteral biologics," confirms Alina Alexeenko, from Purdue University in Indiana, and co-director of the Advanced Lyophilization Technology Hub (LyoHUB)—an industry-led partnership aimed at advancing the science and technology of lyophilization.

Currently, there are an increasing number of biological drugs in development or being approved by regulatory bodies worldwide (2). "Many drugs are unstable in solution," continues Elizabeth Topp of Purdue University, co-director of LyoHUB. "These drugs are often marketed in solid forms to preserve their potency and prolong their shelf-life. This is particularly true for biologics."

It is this growth in biologics that has contributed to the rising importance for lyophilization, they specify. "Unlike other drying methods, lyophilization removes water in a relatively gentle way that helps to preserve the structure and activity of peptide and protein drugs," says Topp.

"For biopharmaceuticals, the increasingly complex molecular formats are very unstable in solution," agrees Sajal M. Patel, associate director, MedImmune. "Lyophilization offers a well-established process that can deliver stable products for parenteral delivery."

Fundamentally unchanged?

The well-established process of lyophilization is considered by many to be both time- and cost-intensive, and has been described as fundamentally unchanged (3). However, according to some experts, these descriptions may not truly reflect the progress that has been made in the lyophilization process over the past few decades.

"The physics may not have changed but our knowledge of the process, equipment, and instrumentation has improved significantly," Thompson stresses.

An improved understanding of the freeze-drying process has led to improvements in the equipment design, Thompson continues to explain. "One such improvement includes the refrigeration systems, which are now properly sized and far more reliable," he says. "Others include condensers that can effectively handle high vapor loads, vapor port designs that don't choke the vapor flow, sterilization methods for GMP processing, loading and unloading automation, and isolators, to name a few."

Not only have there been advances in the instrumentation and control of the process, but also knowledge of the process itself has improved, Thompson adds. "Our understanding of the product critical temperature has improved,

IMAGE: PHIVE2015 - STOCK.ADOBE.COM

for example, which has enabled us to optimize the shelf temperature and chamber pressure to maintain the product just below its critical point while maximizing the sublimation rate," he notes. "Also, the freezing methodology has changed. We now understand that the method of freezing effects the crystal structure in the product."

Understanding of the drying process has also improved. Primary drying, for example, would periodically step up the shelf temperature over time in the past, which resulted in long drying cycles that were susceptible to failing. "We now know that the sublimation rate at the beginning of the cycle can be driven very fast, but as the dry layer builds up in the vial, the sublimation rate is reduced and the product temperature increases, so the shelf temperature needs to be reduced," he adds. "So, today, it is not uncommon to have a high shelf temperature initially and then reduce it for the majority of the cycle, which reduces the primary drying time significantly."

Knowledge of the vacuum level and its effect on the product temperature has also improved. "In the old days, many freeze dryers did not have a method for vacuum control, and often primary drying was attempted at pressures as low as 5 millitorr. It was believed that the lower the chamber pressure the better," Thompson notes. "Today, we understand that the chamber pressure should typically be between 60 and 200 mT for the maximum sublimation rates and for proper process control."

Time and cost considerations

"The literature widely describes lyophilization as time-consuming and expensive," says Patel. "However, both time and expense are relative. It may seem obvious to compare lyophilized drug products to liquid drug products; however, this is an inappropriate comparison as lyophilization is considered when solution stability is unacceptable."

Because many biopharmaceutical products are unstable in solution, time and expense spent on lyophilization could be negligible when considering the total cost of manufacturing biological drugs, Patel explains.

"Regarding optimization of the lyophilization cycle time, there are several publications in the literature addressing this topic," he adds. "Significant progress has been made over the past three decades in terms of heat and mass transfer understanding during the lyophilization process to allow development of the shortest possible lyophilization cycle without impacting product quality attributes. Recent publications (4) demonstrate the application of single-step drying (wherein primary and secondary drying is performed in a single step) that can significantly reduce the lyophilization cycle time."

For Alexeenko, a key reason as to why lyophilization is time-consuming and expensive is that it is currently a batch process with open-loop controls. "An open-loop process is performed using a fixed and often quite conservative recipe," they say. "Conversely, closed-loop processes use immediate feedback from process sensors."

"Processing times for many existing freeze-dried products were developed when our process knowledge was limited, resulting in very long freeze-drying cycles, often lasting a week," notes Thompson. "However, with our current knowledge of freezing and primary drying process dynamics, the processing times can be dramatically reduced—often to less than 24 hours."

Innovation in lyophilization

Overall, industry's goal for lyophilization is to be able to achieve high quality, lower cost, and more readily available lyophilized products, according to Alexeenko and Topp, who led the development of the Lyophilization Technology Roadmap (5), which was released by LyoHUB in September 2017.

"The roadmap, funded through a grant from the US National Institute of Standards and Technology, was the culmination of two years of workshops and meetings involving over 100 contributors who identified lyophilization needs in products, process, equipment, education, and regulatory interface," they add. "It identifies two broad areas of effort needed to move toward improving lyophilization: advancing lyophilization technologies and techniques and strengthening the industry foundation."

Technical innovations will be required across all areas of lyophilization, including the lyophilized products, the lyophilization process, and the lyophilization equipment, they note. "The full implementation of these technical innovations will depend on a strong industry foundation, which will require that the interface between the industry and regulatory agencies be strengthened and that a well-trained workforce be developed and maintained."

For Thompson, significant improvements to assist in the efficiency of lyophilization would come if closed-loop control was employed based on the product temperature rather than the shelf temperature. "Today, the control process is open loop—the shelf temperature is set and controlled and the chamber pressure is set and controlled, but no adjustments are made during the process based on the critical process parameters," he says. "The semiconductor industry uses closed-loop control on all of their processes to maintain consistent quality levels. The pharmaceutical industry needs to begin to adopt the same type of process control to ensure quality and reduce processing times."

Challenges to controlled nucleation

A technique that has been discussed and researched for some time is that of controlled ice nucleation. However, uptake of this technique from a commercial standpoint has been slow. "When controlled nucleation was first introduced it was over-marketed as a methodology to reduce primary drying time," states Thompson. Although it is a technique that is widely available in laboratory freeze dryers, he adds that there are certain road blocks to its implementation within mainstream production.

"There have been significant advances in using controlled ice nucleation in research and development, with over 250 publications on controlled ice nucle-

ation since 2010 (about half of them in the past three years). However, there is still a need for integration of ice nucleation technology in validated manufacturing processes," agrees Alexeenko.

Patel also concurs with the challenge of availability of controlled ice nucleation at the production scale. "It's difficult to modify existing freeze-dryers, and new facilities are reluctant to adopt the technology with the argument that controlled nucleation is 'nice to have' but not a 'must have'," he says. "Controlled nucleation cannot be implemented in early development because there are not many manufacturing facilities that have controlled nucleation capability."

"The major benefit for controlled nucleation is to produce a consistent ice formation across the batch at the beginning of the freezing cycle," summarizes Thompson. "Consistency across the batch improves the quality of the finished product. I believe that the best way to justify implementation of controlled nucleation is to improve the quality and consistency of the finished product. If it also reduces process times, it is an added bonus."

The importance of PAT

Experts agree that process analytical technology (PAT) is important in the advancement of lyophilization. "PAT is an integral part of the lyophilization process design, development, optimization, and scale-up," emphasizes Patel. "The information gained about the process performance and the understanding of parameters that could potentially impact product quality are key to building quality within the product rather than testing quality at the end of the process."

PAT is also vital for industry to achieve closed-loop control in lyophilization, notes Alexeenko. "Many new PAT solutions are being developed and applied now, especially for direct measurement of product temperature, *in-situ* measurement of lyophilization rate, and tracking non-aqueous solvents in complex formulations," she adds.

Thompson, however, stresses that the definition of PAT needs to be clear. "PAT is a technology that provides direct measurement of the critical process parameters in real time for process monitoring and control," he says. "Users need to understand that many of the PAT tools being offered by manufacturers provide information based on indirect measurements and calculations based on assumptions. Many of the tools provide 'batch average' information, which does not provide the resolution needed to understand the process variations across a batch of vials."

And what about cake appearance?

A rather controversial topic that has been the subject of much debate over the years is that of cake appearance. "The common misunderstanding is that the end user demands a good look and feel for a lyophilized product or that in certain markets, 'pharmaceutical elegance' is critical," explains Patel. "However, there are no data to support any of these misunderstandings. On the contrary, some of the experiences shared within the industry suggests otherwise (6)."

In partial agreement, Thompson states that cake appearance is very subjective and in fact, a poor cake appearance is not an indicator of an improperly freeze-dried product or poor drug substance. "However, a doctor who takes a vial and is adding water before injection would be very concerned if the cake appeared to be collapsed. They cannot be sure whether the product was exposed to high temperatures or the seal on the vial was compromised," he says. "New studies show that in some cases, product that has collapsed during freeze drying may result in more stable product that can be fully reconstituted (7). The challenge is whether the doctors in the field will trust the product."

A change in mindset is needed

"Our knowledge and understanding of lyophilization has evolved significantly over the past three decades, particularly in terms of impact of formulation and process on product quality, and active research in the field would further enhance our understanding of the lyophilized drug product," summarizes Patel.

"However, our progress in the field of lyophilization demands a change in mindset," he states. "Lyophilization is an established process to deliver a sterile product with existing infrastructure."

There are several innovations in lyophilization already under development, notes Topp. "These include continuous lyophilization, which could increase the efficiency and throughput of the process; wireless sensors, which would allow for better control of the process and support continuous processing with closed-loop control; computational monitoring, which would allow for better design of lyophilization equipment and facilitate scale-up; and analytical methods, which are enabling more rapid development of lyophilized products and can support manufacturing by evaluating the effects of process deviations on the product," she asserts.

"With these advancements, as well as those in PAT tools, lyophilization can be monitored and controlled to minimize processing time and cost," adds Patel. "But, more importantly, lyophilization can deliver a quality product that is stable for commercialization."

References

1. Research and Markets, "Lyophilization Services for Biopharmaceuticals, 2017–2027," report ID: 4229083, April 2017.
2. F. Mirasol, *BioPharm Int.*, 31 (3) 14–17 (2018).
3. PharmTech, "Experts Set a 10-Year Roadmap for Optimizing Lyophilization," Sep. 14, 2017 www.pharmtech.com/experts-set-10-year-roadmap-optimizing-lyophilization-0, accessed Jan. 3, 2019.
4. S.K. Pansare, and S.M. Patel, *J. Pharm. Sci.*, Nov. 20, 2018. pii: S0022-3549(18)30725-1. doi: 10.1016/j.xphs.2018.11.021. [Epub ahead of print].
5. LyoHUB, "LyoHUB Roadmapping," pharmahub.org, https://pharmahub.org/groups/lyo/lyohub_roadmapping, accessed 3 Jan 2019.
6. S.M. Patel, et al., *J. Pharm. Sci.*, 106 (7) 1706–1721 (2017).
7. E.E. Etzl, G. Winter, and J. Engert, *Pharm. Dev. Technol.*, 19 (2) 213–222 (2014), DOI: 10.3109/10837450.2013.769567. **PT**

Spectroscopy Facilitates Lean Analysis

John Wasylyk, Ming Huang, Bob Wethman, and Kieran O'Connor

The biopharmaceutical industry is responding to the need for accelerated development timelines of new medicines and identifying opportunities to accelerate development and optimize the manufacturing process. Spectroscopic-based controls have been demonstrated to be quicker, more flexible, and easier to operate and automate than traditional analytical control applications. This paper describes two separate case studies in which spectroscopic methods were introduced as equivalent alternative methods, first to a gas chromatographic method to monitor an in-process solvent exchange step and second to a potentiometric titration method to release a process input material. The spectroscopic techniques implemented were Raman and Fourier transform near infrared (FT-NIR) spectroscopy. The implementation of the spectroscopic methods generated significant increases in sample throughput as well as reductions in plant cycle time, analysis times, and incidences of analytical deviations.

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The Food and Drug Administration (FDA) Safety and Innovation Act of 2012 (1) established a breakthrough designation program to expedite the development and approval of innovative drugs for serious and life-threatening conditions. As biopharmaceutical companies have identified the potential to file new drug entities as breakthrough designation candidates, they need to concurrently identify opportunities and strategies that will allow them to accelerate the development process and optimize manufacturing. FDA and other regulatory authorities are encouraging the industry to adopt a more risk-based, scientific approach to drug development and manufacture, as detailed in the FDA Guidance for Industry document *Process Validation: General Principles and Practices* (2) and the International Council for Harmonization (ICH) Q8, Q9, Q10, and Q11 documents (3–6). These documents detail techniques, procedures, and strategies by which increased process knowledge and understanding, and ultimately greater process control, are obtained. These advances are accomplished through comprehensive development activities, including creation of a process design space, thorough and challenging risk assessments, and use of process analytical technologies (PAT) to develop critical process parameters (CPP) for control. The knowledge obtained through these approaches can subsequently be applied to risk-based decisions to accelerate the development process.

Bristol-Myers Squibb (BMS) actively embraces this risk-based approach to drug development and manufacture and has established PAT-focused research groups within both drug substance and drug product development to enable robust data generation and process understanding. The Enabling Technologies Group (ETG), within the Chemical and Synthetics Development department, specializes in the development and implementation of spectroscopic-based methods for process monitoring of pharmaceutical and biopharmaceutical drug substance development and manufacture. The ETG collaborated with BMS Ireland's small-molecule drug substance commercial manufacturing site (which changed ownership to become SK biotek Ire-

land in January 2018) to identify opportunities to introduce spectroscopic-based methods of analysis to generate richer batch data sets and increase the overall efficiency of the site manufacturing operations.

One unit operation that was quickly identified as an opportunity to increase the efficiency of both the plant cycle time and the quality control (QC) laboratory was the monitoring of solvent "swaps" or exchanges in the reactors. Solvent exchange is one of the most common unit operations in a drug substance manufacturing facility, as solvents routinely need to be removed for multiple reasons, such as for compatibility with subsequent reaction steps, to facilitate crystallization, and/or to purge impurities. The team evaluated the solvent exchanges used in the production of the high-volume products that the site manufactured for opportunities to implement spectroscopic-based methods. These opportunities would afford the greatest gains in plant and laboratory efficiency. The target identified was an in-process solvent exchange step that employed gas chromatography (GC) as an in-process control (IPC) test. The overall impact to the plant cycle time was significant, as the reactor needed to be cooled to a safe temperature before a sample could be taken and transferred to the QC laboratory where the sample analysis and data processing takes approximately two hours to complete before the result is communicated back to the manufacturing team. Thus, the following steps all contributed to the overall time for this IPC: cooling the reactor, sampling the reactor, transferring the sample to the QC lab, preparation of GC instrument and analysis of system suitability solutions, analyzing the sample, reviewing the data, reporting the results, and re-establishing the reactor temperature.

The ETG identified this IPC as being suitable for Raman analysis, as both of the solvents (dichloromethane [DCM] and acetone) generate significant and distinct responses in the Raman spectrum. A two-part plan was devised with the local analytical group. This plan was to initially develop and validate an at-line Raman method for the solvent exchange analysis as an equivalent alternative to the GC analysis and then subsequently introduce an equivalent, in-line Raman method. Once the team had demonstrated the feasibility of the at-line method, the second part of the plan, an in-line approach, was implemented. The rationale for the in-line analysis was to further improve process throughput, as the at-line Raman analysis still required that the reactor be cooled before sampling. An in-line analysis was developed using a Raman probe (Pilot E, Kaiser Optical Systems) that was placed directly in the reactor. The results were exported directly to a distributed control system (DCS) in the plant, realizing additional time savings through the elimination of the cooling and sampling steps.

In addition, the team identified an opportunity to enhance the plant efficiency by using spectroscopy for the molarity determination of hydrochloric acid in methanol (HCl in MeOH), a key reagent used in the manufacture of one of the drug substance processes run on the site. The plant had been determining the molarity using potentiometric titration, and the testing was required for both QC release testing of the reagent as well as an IPC test during batch processing. Despite the simplicity of titration testing, it was a time-consuming test that took a number of hours to complete because solutions needed to be prepared and standardized prior to sample analysis. FT-NIR was identified as an appropriate spectroscopic technique for the development of an at-line method. A method was developed and validated and then introduced as an equivalent alternative to the titration method, achieving greater than ten-fold reduction in sample turnaround time, as described in case study 2.

Case study 1: solvent exchange monitoring using Raman spectroscopy

As described in the previous section, GC analysis for the solvent exchange step in the manufacture of a drug substance was being used to perform the IPC test. The total analysis time in the QC laboratory typically took approximately four hours to complete, including instrument setup, standard and sample preparation, analysis of system suitability, working standard, blank and reaction completion sample solutions, processing of the relevant data using chromatography data software (Empower, Waters), and the documentation review and approval. Because both solvents (DCM and acetone) possess strong Raman responses with unique and characteristic bands, Raman was a suitable spectroscopic technique for monitoring the solvent exchange.

At-line Raman analysis. Feasibility trials were performed using an analyzer (RXN2 Raman-785 nm, Kaiser Optical System) equipped with a HoloLab Analytical Sample Compartment (HLSC, Kaiser Optical System). Sample and standard solutions were analyzed in glass cuvettes. The absence of interfering fluorescence or other matrix effects was confirmed using process sample solutions.

A multivariate analysis model was developed that employed the ratio of the DCM peak response divided by the sum of DCM and acetone peak responses. Based on this simple model, a linear curve was established, bracketing the IPC specification for the solvent exchange, and was applied to the reaction samples.

Validation. Validation was successfully performed following ICH Q2(R) guidelines (7) and using the GC method as the primary reference method. Validation tests performed included specificity, linearity, limit of detection, precision, and accuracy. An equivalency protocol, in which process samples were analyzed by both the GC and Raman methods and the results from both data sets were compared against each other using predefined acceptance criteria, was also successfully performed. The Raman method was then introduced into the QC laboratory as an equivalent alternative to the GC method. Appropriate training and ongoing technical support were provided to the IPC chemists to ensure the Raman analysis was effectively introduced into the labora-

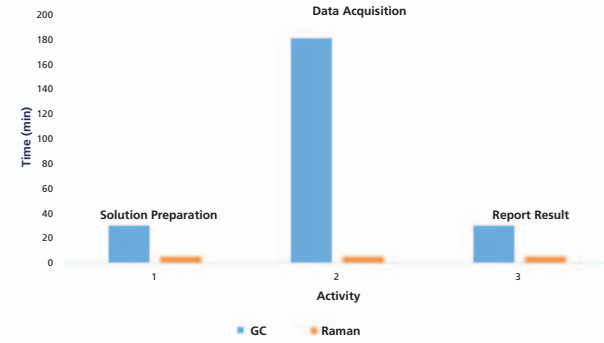
tory. The relevant regulatory filings were updated to include the application of the Raman analysis as an equivalent alternative to the GC analysis, thereby enabling use of the Raman analysis for commercial release.

The introduction of the at-line Raman method into the QC laboratory was successful, with QC chemists quickly understanding and appreciating the benefits of this mode of analysis. Key factors in the successful introduction were focused and concise documentation (including test methods, work instructions, etc.), a thorough and comprehensive training program, and the straightforward execution of the analysis. The sample analysis involved the placement of the sample in the HLSC and running the method on the RXN2 analyzer. Sample analysis time for the Raman analysis was 15 minutes compared with 240 minutes for the GC analysis, thereby enabling a significant reduction in result turnaround time using the Raman analysis (see **Figure 1**).

Model maintenance. It is important to demonstrate the continuing validity and accuracy of the chemometric model used in the spectroscopic method at regular time periods throughout the lifecycle of the method. This maintenance is necessary to account for the following: potential changes in vendors (which may utilize alternative synthetic routes for process reagents and solvents), instrument/model drift over time, and changes in the process manufacturing route. Validity is typically achieved by applying a change-control protocol and a model maintenance program to the chemometric model. Model maintenance for this IPC method involves repeating selected validation tests (e.g., specificity, accuracy, and precision) periodically, using the GC method as the primary reference method. The activities are documented in a protocol that is included in the maintenance report. Maintenance is performed annually or following any significant changes to the manufacturing process or raw material supply that are prompted by change-control actions.

In-line analysis. The introduction of the at-line Raman method resulted in reduced sample analysis times, reduced consumables for analysis (solvents, glassware), and increased sample throughput in the QC laboratory. As a result, the team assessed the feasibility of introducing an in-line application for the process to achieve even further savings by eliminating the need for cooling the reactor and sampling the reaction. Based on the high commercial volumes and the need to run frequent manufacturing campaigns, it was identified as an opportunity to save significant plant cycle time with a positive return on investment. The proposed in-line solution would involve the installation of a Raman probe (Pilot E, Kaiser Optical Systems) in the reactor, which would allow the reaction to be sampled directly in the reactor and eliminate the need to cool it. In addition, the processed IPC result would be automatically transferred to the DCS as part of the batch record. A cross-functional team comprised of representatives from manufacturing, engineering, analytical, information technology, and quality was assembled to perform a failure-modes effect analysis on the process step.

Figure 1: Comparison of gas chromatography (GC) and Raman spectroscopy analysis times.



Areas that were analyzed included in-line monitoring infrastructure requirements, mode of result generation and results reporting into the DCS, qualification and validation requirements, and equivalency/comparability requirements for the in-line analyzer.

The in-line application included developing an equivalent analysis model for an ATEX-rated Raman analyzer (RXN3-785, Kaiser Optical Systems) and acquisition of Raman spectra from the reactor vessel via a Raman probe (Pilot E, Kaiser Optical Systems) connected to the analyzer using fiber optic cables.

Equivalency between the at-line and in-line models was demonstrated using an equivalency protocol based on the data generated from the at-line and in-line models for in-process samples from the same reaction. Software (SynTQ Lite, Optimal Industrial Automation) was applied to the analyzer to provide a 21 *Code of Federal Regulations* (*CFR*) Part 11-compliant operating platform. Results generated were automatically exported to the DCS, which enabled real-time decisions to be made regarding progression of the manufacturing process. This installation eliminated the requirement to cool down the reactor, remove a sample, and perform an at-line analysis in the IPC laboratory, thereby generating even greater manufacturing cycle time gains.

Process knowledge obtained by observing real-time Raman trends during the solvent-exchange step resulted in a temperature-control step being added to the manufacturing batch record to ensure the product remained in solution, which further improved batch throughput. The knowledge was obtained through investigating irregular DCM concentration profiles during the solvent-exchange step using the in-line Raman probe. Negative concentration results were being reported, and upon review, it was noted that the raw Raman spectra were atypical for the negative concentration results. At-line analysis of the reactor supernatant displayed typical concentration results for DCM. The irregular profiles were typically generated in the early morning during the winter/spring season. The process solvent (acetone) was stored in an outside tank and was introduced into the reactor

FIGURE IS COURTESY OF THE AUTHORS.

through pipework that was exposed to the outside elements. There was no temperature control of the reactor lagging jacket. Following a thorough review of the parameters of the process (e.g., time of year, external tank, and bulk process solvent being added in large volumes), it was hypothesized that the bulk acetone was being added at a sufficiently low temperature to cause the product to precipitate out of solution, which impacted the Raman scattering effect and generated the negative concentration values. A corrective measure introduced to counteract this effect was to introduce a temperature control of not less than 18 °C to the reactor lagging jacket. Following the introduction, the irregular DCM concentration profiles were no longer observed, which improved batch throughput.

Case study 2: HCl molarity determination using FT-NIR

A second opportunity identified to leverage spectroscopic-based methods to enhance the efficiency of the manufacturing plant and QC laboratory was the analysis of critical reagents and solutions. All reagents that are used in the commercial manufacturing process require release testing. In addition, many solutions that are prepared from these reagents will typically require an in-process release test before they can be used on the plant floor. The team identified the reagent HCl in MeOH as an application that might be suitable for analyzing using a spectroscopy-based alternative method. Because solutions of HCl in MeOH are hygroscopic and readily degrade on exposure to air, a rapid and accurate method was required to ensure that the correct concentration of reagent was being added to the reaction for each batch. The regulatory filed process called for the concentration of solutions of this reagent to be determined using simple acid/base titration. Despite the simplicity of this analytical technique, the analysis typically required over six hours from start to finish to generate and approve a result. This length of time was due to the numerous steps involved, including gathering the necessary glassware, solvents, and reagents; preparing and standardizing the various solutions; analyzing the sample; calculating the result manually; and reviewing and approving the result. The in-process analysis of this reagent solution had been identified as a process bottleneck, and the team assessed the option of introducing an equivalent spectroscopic method of analysis that could generate a result in a more expeditious manner. Based on initial feasibility studies including Raman, FT-IR, and FT-NIR, FT-NIR spectroscopy was identified as an appropriate technique for analyzing commercially sourced solutions of HCl in MeOH. The rationale for the selection of FT-NIR included sensitivity and selectivity for the compound of interest, ability to generate quantitative models, and availability of identical instrument models at both sites.

Results were generated using an analyzer (Antaris II FT-NIR, Thermo Scientific) in the transmission mode. The molarity of the reagent was determined using a partial least-squares chemometric model. The resulting FT-NIR method was capable of generating sample results in only two minutes. This short analysis time was enabled by embedding the chemometric model into the method, requiring only a single sample scan be acquired to generate a result. The analytical team at the BMS Ireland commercial manufacturing site had purchased an identical instrument to the one used by the ETG in the United States as part of the collaboration between the two groups. It had been previously recognized that alignment of both hardware and software components of the instrumentation at both sites would enable more effective knowledge transfer and troubleshooting/optimization activities, as well as enhance technology transfer of analytical methods.

Method transfer. Transfer of the FT-NIR method to the manufacturing site was conducted following the co-validation mode of technology transfer as defined by *United States Pharmacopeia* <1224> (8). Validation tests performed per ICH Q2 (R1) guidelines including specificity, linearity, repeatability, accuracy, and limit of detection/limit of quantitation (7). Acid/base titration analysis was used as the primary reference method during the validation. A comparability protocol was also successfully completed, in which 10 different lots of HCl in MeOH were analyzed using both the primary titration method and the secondary FT-NIR method and the results generated compared against predetermined acceptance criteria. Upon conclusion of the co-validation and comparability protocol testing, the results were summarized, and a proposal was submitted to the BMS Ireland site quality assurance function to introduce the FT-NIR method as an alternative equivalent to the titration method. The proposal was accepted, and the necessary activities to introduce the method, including raising a change control action, issuing of the test method report, and training the QC and IPC chemists were performed.

The acceptance of the introduction of the FT-NIR method has been uniformly positive from the process and analytical team members. Analysis is straightforward: the analyst decants the sample solution into a 2-mL vial, places the vial in the transmission cell of the spectrometer, and selects the appropriate workflow. A result is automatically generated by the instrument within two minutes. The ease of use and rapid result generation is well suited for the in-process control environment because it enables a result to be provided back to the process chemists within minutes of sample submission. Using the previous titration method, the processing team could be waiting hours for results, resulting in significant plant idle time.

Model maintenance. As with the Raman model detailed in case study 1, model maintenance is performed by repeating the validation tests using the primary titration method on an annual basis. If the site change-control management system captures any changes to the reagent supply parameters, instrument operation, or drug-substance manufacturing description that could impact the accuracy and validity of the partial least-squares model, model maintenance is triggered.

The introduction of the FT-NIR method in the commercial setting was successful. Result turnaround times were more than 10 times quicker than with the titration method, which was particularly beneficial to the in-process control work stream because it simplified analysis and facilitated improved manufacturing throughput times for this process, while at the same time freeing up analyst time in the QC laboratory to work on other high priority issues. As a result of the benefits and efficiencies gained through the introduction of the FT-NIR method for HCl in MeOH, the site identified three additional reagent concentration IPC methods that were creating bottlenecks in the plant workflows. Alternative, equivalent FT-NIR methods have subsequently been developed and introduced into the QC laboratory, resulting in faster turnaround times, simplified sample analyses, and a reduction of the resource demands in the laboratory.

Conclusion

The adoption of spectroscopic-based methods can improve the efficiency of analytical operations both within the plant environment (i.e., in IPC) and the QC laboratory. The two case studies highlight the time savings and analytical throughput increases obtained by introducing Raman spectroscopy as an alternative equivalent method to GC for solvent exchange monitoring and FT-NIR spectroscopy as an alternative equivalent to titration analysis for process reagent analysis.

In the Raman spectroscopy case study, significant efficiencies were obtained using both in-line and at-line applications. This example highlights an effective strategy for the introduction of spectroscopic technologies to a laboratory/manufacturing site. Initially introducing the at-line application to the site enabled the staff and management to gain a fuller understanding and appreciation of the advantages of the technology with a modest investment of time and effort. The subsequent introduction of the in-line application was achieved with strong support of management due to the prior experience with the at-line application.

The ease of use and ruggedness of the at-line applications facilitated enthusiastic uptake and ownership of the technologies by the laboratory chemists. At-line spectroscopic applications can facilitate improved analytical performance while minimizing the need for large resource investments, infrastructure, and maintenance activities associated with in-line/PAT applications. In addition, the at-line applications generated significant analytical operation efficiencies through improved sample throughput; reduction in analysis time, laboratory errors, and laboratory waste; increased laboratory capability; versatile analysis; and the capability to automate and network.

Acknowledgement

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References

1. FDA Safety and Innovation Act (FDASIA) Section 902, 126 STAT. 993, Public Law (July 2012), pp. 112–144.
2. FDA, *Guidance for Industry, Process Validation: General Principles and Practices* (Rockville, MD, 2011).
3. ICH, Q8 (R2) *Pharmaceutical Development* (ICH, 2009).
4. ICH, Q9 *Quality Risk Management* (ICH, 2005).
5. ICH, Q10 *Pharmaceutical Quality System* (ICH, 2008).
6. ICH, Q11 *Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)* (ICH, 2012).
7. ICH, Q2 (R1) *Validation of Analytical Procedures: Text and Methodology* (ICH, 1997).
8. USP, General Chapter <1224> "Transfer of Analytical Procedures", *USP 39-NF 34*, pp.1638. **PT**

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As Technology Advances, Annex 1 Falls Short

Agnes Shanley

Robotic isolators and single-use technologies are gaining ground, according to aseptic processing consultant Jim Agalloco.

Aseptic manufacturing, and particularly fill and finish operations, continue to challenge pharmaceutical manufacturers. Consultant and *PharmTech* Editorial Board advisor Jim Agalloco discussed industry and technology trends and regulatory challenges with *Pharmaceutical Technology*.

Adoption of advanced technology

PharmTech: Have you seen any change in how the industry is using advanced aseptic manufacturing technology?

Agalloco: One trend that is moving very quickly is the use of robotics in isolators, eliminating the need for gloves, so that less human intervention is needed than there ever was. VanRx has taken this to an extreme with its gloveless isolators; other equipment manufacturers are moving in the same direction, including AST, IMA, Fedegari, and Aseptic Technologies. Currently, this robotic equipment runs at lower speeds than traditional equipment, but robots don't take breaks or lunch so there is a lot of potential benefit. The essential first step was moving to closed systems, after that, vendors and end users can work on making them run faster.

We are also seeing explosive growth, even faster than the growth of robotics, in the use of single-use disposables within aseptic manufacturing. The idea is to take away the stainless steel piping and rigid lines, so that there is one connection from product supply all the way to the fill needle.

Using disposables requires collaboration between single-use system vendors and equipment manufacturers, who must integrate single-use components into their filling controls and get them to work properly. This approach eliminates the need to clean and keep so many parts in inventory and reduces cost and contamination risk. Single-use systems are going into high-speed filling lines and into robotic closed systems.

PharmTech: Has there been any change in the scope of services that aseptic equipment vendors are offering pharma customers?

Agalloco: We are seeing an alignment of supply chains so that vendors are doing much more of the upstream work that manufacturers used to have to do. For example, many equipment vendors are now providing pharmaceutical manufacturers with prewashed, presterilized, and predried glass, syringes, closures, and stoppers.

This approach reduces the end user's facility and personnel needs and puts more responsibility on suppliers. Vendors are taking the lead in this change.

Impact of mergers

PharmTech: Are the mergers and acquisitions that have occurred in the contract manufacturing space over the past few years having any impact on aseptic operations within the industry?

Agalloco: Contract manufacturing organizations (CMOs) are getting larger. More pharmaceutical manufacturers want to work with one partner from small-scale to commercial manufacturing to reduce the number of hand offs. This trend also ensures that CMOs have sufficient resources. Poor performers are being weeded out.

PharmTech: Is compliance improving?

Agalloco: CMOs are getting better and more players are getting into this space. However, major pharma companies continue to struggle and much of this is directly attributable to aging facilities. Anywhere you see an older plant you are likely to see problems. Generic injectables and vaccines sell with next to no profit, but modernizing manufacturing or replacing a facility could cost $200 million or more.

PharmTech: Is the emphasis on generic drugs creating this problem?

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Agalloco: Drug shortages are merely the result of issues with cost control that came out of the approval of generic drugs. These issues have developed over 30 years as facilities have aged, and prices have fallen. Very simple drugs are in short supply because nobody invests in them when the margins are so thin. I am terrified about biosimilars, because now we are taking even more complex processes and making them cost competitive.

"The more 'how tos' regulators put into their expectations, the less innovative we become."

— Jim Agalloco

PharmTech: Are you seeing greater acceptance of innovation in pharma?

Agalloco: As far as adopting innovative technologies, pharma is still a laggard industry, especially on the sterile side. Even though the FDA's Emerging Technology Team (ETT) has included advanced aseptic technology in its agenda, some equipment innovators struggle with a Catch-22: Regulators won't review a new technology unless it is used in a drug submission, and no drug manufacturer will invest in the technology if no other drug manufacturer has previously used it and had a drug approved with it.

PharmTech: Do we need new guidances on aseptic manufacturing?

Agalloco: No. Guidances can become a barrier to improvement. FDA regulations work because they tell you 'what to' and not 'how to'. The more regulators put 'how tos' into their expectations, the less innovative we become.

PharmTech: What are your thoughts on Annex 1 (1), the European Union (EU) draft guidance?

Agalloco: Annex 1 represents one of the EU's first efforts to develop guidance in an open way with the industry, but they won't get it right in one pass. Industry submitted thousands of critical comments, and my colleagues, James Akers and Russell Madsen, and I submitted over 170 comments (2).

Problems with Annex I

PharmTech: What are the most glaring problems in the draft guidance?

Agalloco: Apart from the way it is written and organized, my colleagues and I take issue with the fact that the draft presents a view that conflicts with existing and established global regulations, standards, and compendia (e.g., US and Japanese guidance on sterile manufacturing). For example, the document does not incorporate the requirements established by International Organization for Standardization (ISO) 14644, and perpetuates a myth that microbiological testing can improve sterility assurance (3). The document also uses an antiquated and arbitrary classification system, rather than ISO 5, 6, 7, and 8 categories.

In addition, the draft does not incorporate the most modern and appropriate guidance for sterile product preparation, as outlined in *United States Pharmacopeia (USP)* Chapters 1211, 1228, and 1229 (4–6). Classification of controlled environments should be limited to non-viable particle monitoring as described in ISO 14644, and not based on microbial enumeration.

Furthermore, the guidance presents an unscientific view of microbial monitoring. The limit of detection for microbial testing is much higher than one colony forming unit, as the document now states. As a result, it may overstate the value of environmental monitoring in manufacturing sterile medicinal products. Its language also conflicts with the European Medicines Agency's (EMA's) guidance, specifically its water for injection (WFI) Q&A paper (7), and *Guidelines on Good Manufacturing Practice Specific to Advanced Therapy Medicinal Products* (8).

PharmTech: How does it cover cleanrooms and advanced technologies?

Agalloco: The document groups conventional cleanrooms, restricted access barrier systems (RABS), and isolators together, even though these technologies are demonstrably different in many ways. This approach diminishes the performance of isolators, inflates RABS capabilities, and fails to consider adequately the limitations of barrier-equipped manned cleanrooms.

PharmTech: How does the document approach the topic of validation?

Agalloco: The draft guidance asks for testing of materials, containers, and surfaces, as if expecting testing alone to assure product quality. The core principle behind validation is to assure confidence in a process' reliability and appropriateness in ways that testing alone cannot do. Misplaced emphasis takes us back in time.

References

1. R. Madsen, J. Agalloco, and J. Akers, "Annex 1–Misses the Mark," *Pharmaceutical Technology Europe* 30 (2) (201)
2. European Commission, *EudraLex, Volume 4, EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use,* Annex 1, Manufacture of Sterile Medicinal Products, December 2017.
3. International Standards Organization, *ISO 14644–Cleanrooms and Associated Controlled Environments—Part 1: Classification of Air Cleanliness by Particle Concentration*, 2015.
4. USP, General Chapter <1211>, Sterilization and Sterility Assurance of Compendial Articles, *USP-NF* (US Pharmacopeial Convention, Rockville, MD, 2017).
5. USP, General Chapter <1228>, Depyrogenation, *USP-NF (*US Pharmacopeial Convention, Rockville, MD, 2017).
6. USP, General Chapter <1229>, Sterilization of Compendial Articles, *USP-NF* (US Pharmacopeial Convention, Rockville, MD, 2017).
7. European Medicines Agency, EMA/INS/GMP/443117/2017, *Questions and Answers on Production of Water for Injections by Non-Distillation Methods–Reverse Osmosis and Biofilms and Control Strategies*, August 2017.
8. European Commission, *EudraLex, Volume 4, EU Guidelines on Good Manufacturing Practice Specific to Advanced Therapy Medicinal Products*, November 2017. **PT**

Fundamentals of GMP Warehouse Design

Eric Bohn and Magdalena Krapf

Storage and retrieval methods and the unique requirements found in building codes are crucial considerations.

Warehousing is a crucial yet often-overlooked need of the pharmaceutical industry. Although GMP warehousing can have some specific requirements (e.g., cleanliness, temperature control), some of the same basic questions and criteria drive warehouse design for both GMP and conventional warehouses.

Considering storage and retrieval methods

An effective warehouse must be appropriate for the materials being stored. Likewise, a sound understanding of the inventory is necessary to create an efficient and successful operation. Not only do the materials anticipated need to be identified, but the frequency, quantity, and sequence of retrieval must be considered.

Choosing a pallet rack type. The key attribute of warehousing is the method of storage; in other words, the type of pallet rack that is used. There are many options available; some of the common types are known as "single or selective," "double deep," "push back," "drive-in," and "flow racks". Fundamentally, however, the decision for the most appropriate rack focuses on the number of pallets stacked within a horizontal lane of the rack.

Placing pallets one deep on a multilevel rack is the traditional and most common approach. This approach provides the greatest flexibility because it gives access to all pallets, at all times. The relative low density of pallets, however, limits the quantity that can be stored. Greater density is achieved by increasing the height of the racks or by placing pallets one behind the other within the same lane. Verticality is a function of the height available; lane depth is driven by the materials stored and the rate of their use. For any given height, stacking pallets more than one deep eliminates aisles and increases both the pallet density per square foot and the amount of storage.

When stacking pallets one in front of the other, however, a condition referred to as "first in, last out" is created. The pallet in front must be used before the one behind is available. To justify this method of storage, all the material in that lane must be the same, and the quantity and rate of use needs to be such that the "last" pallet is taken in a timely manner. To store pallets that are never used is an obvious waste of space, inventory, and money. The number of stock-keeping-units (SKUs), the throughput, and inventory turnover all play into this decision. A warehouse, of course, does not need to have only a single type of racking. An analysis of the inventory will also provide the data necessary to determine the diversity and appropriateness of multiple types of rack.

Considering forklifts and aisle spacing. In selecting racking, the type of fork truck must also be factored. There are numerous types of trucks, each with different performance characteristics and capital costs. Characteristics include height and depth of reach; sit-down, standing, and "man-up" models as well as the space required for maneuvering. Conventional, sit-down, counterbalance forklifts require a turning radius of up to 13 feet. To allow turning and placement of loads in the racks, this maneuvering dimension must be provided in front of the racks. But there are other options. At the other extreme, a special turret truck is offered that allows narrow aisles of as little as six feet between racks. In large facilities, considerable density can be achieved through these smaller aisles.

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When considering aisles, however, the width needs to work in concert with the column bays. For those fortunate enough to build a new facility, it is possible to optimize these three factors: rack types, forklift, and column spacing. When working in existing facilities, however, the column spacing is a given, and some compromises are often required.

Contemporary supply-chain strategies try to balance the quantity stored to the throughput of the facility.

Automated systems. High-density warehousing with automated storage and retrieval systems (AS/RS) offers a solution for many warehousing challenges. These computer-controlled systems use neither aisles nor forklifts. Each pallet is automatically placed and retrieved from defined storage locations on robotic carriages. AS/RS maximizes storage within a given footprint, reduces labor costs, reduces product damage, and increases the accuracy of inventory management, but capital costs are significant.

The physical storage of pallets, as basic and simple as it appears, has not been overlooked by the digital revolution. Software to manage and control inventory can greatly reduce costs. It is easy to assume that more storage is better. Large inventories, however, require money tied up in idle materials that are not adding value, and the capital costs to construct and operate larger warehouses must be considered. Contemporary supply chain strategies try to balance the quantity stored to the throughput of the facility. With barcoding and radio-frequency identification, it is possible to know every item in an inventory as well as its real-time status. Production planning and historical data can be used to reduce the time that materials are stored before use. This "just-in-time" approach contrasts with the traditional "just-in-case" philosophy. Efficiency is increased and waste decreased by receiving goods only as needed. Less space is used, smaller inventory investments made, minimal inventory obsolescence occurs, and responsiveness for accommodating product changes is increased.

Considering building codes

In addition to these fundamental programmatic considerations for storage and retrieval of materials, key building code issues must be considered when designing GMP warehouse facilities.

Material classification. The first consideration for code compliance in a warehouse is understanding what is being stored. The materials must be identified, and their classification determined. Commodity Class is a classification system that is understood by fire protection engineers and is defined in several standards, most notably the National Fire Protection Agency's NFPA 13 (1) and the International Fire Code (IFC), Section 3203 (2). When determining the Commodity Class, more than just the material stored needs to be considered. The packaging and pallets must also be included. In pharmaceutical warehouses, raw materials and finished goods usually fall into Commodity Classes III and IV, which include wood, paper, and certain plastics. The following comments, being focused on GMP warehouses, assumes a Commodity Class of III and IV.

Storage configuration. The next critical parameter in determining code requirements is the amount and configuration of the storage. As illustrated previously, pallets can be stored on the floor or even stacked. But racking of pallets is the most efficient form of storage and almost the definition of a warehouse. Providing racking configured to include a flue space behind the pallet load is important. Racks with a flue will eliminate the need for in-rack-sprinklers, which are expensive and an inefficient use of capital.

Storing materials above 12 feet in height is a significant benchmark. Above this height, racking becomes defined as high-piled combustible storage. The IFC addresses high-piled combustible storage and defines it as "Storage of combustible materials in closely packed piles or combustible materials on pallets, in racks or on shelves where the top of storage is greater than 12 feet" (2). A result of the high-piled combustible storage found in warehouses is the requirement for fire apparatus access roads around the building. Because of the increased fire hazard that high-piled storage represents, ready access by fire trucks is crucial for life safety and property protection. To this end, the IFC requires that an access road configured for fire trucks with a minimum width of 20 feet must be located such that all portions of the exterior walls of the warehouse are within 150 feet of the road. This ensures that the local fire department is able to attack a potential fire from all sides of the warehouse exterior.

The next benchmark relates to the size of the warehouse. Once the floor area of the high-piled storage reaches 12,000 ft^2, there are additional considerations that need to be met. Automatic sprinklers and fire detection systems are required as well as smoke and heat removal. In addition, access by fire department personnel are mandated. Above the 12,000-ft^2 threshold, the IFC requires, in Table 3206.2, that smoke and heat removal be provided (2). This can consist of smoke/heat vents or a mechanical smoke evacuation system. However, smoke and heat removal are expensive and often considered undesirable. When an early suppression fast response (ESFR) sprinkler system is provided, an option exists where smoke and heat removal can be avoided. Although an ESFR system also represents an expense, because it is so effective at extinguishing a fire, it is usually considered a sound investment.

Exceeding the 12,000-ft^2 limit also mandates increased access by the fire

department. In addition to accessibility for fire trucks, as previously mentioned, the increased hazard requires firefighting personnel have direct access to the building interior. Conventional three-foot-wide, swinging personnel doors provide this building entry. Along the exterior walls that face the fire truck access roads, doors for entry of fire personnel need to be located no more than 125 feet apart. Each of these doors must be clearly identified and a key box installed adjacent. This ensures that firefighters can easily get to and gain access to the interior when needed. It should be noted that loading dock doors are not as easily accessed, and therefore, the code does not allow them to be used as fire personnel access.

As discussed, rack storage can exceed 40 feet in height. But Chapter 32 of the IFC provides a dimensional limit of 40 foot for high-piled combustible storage. Above this height, the code redefines storage as extra-high-rack combustible storage. Extra-high-rack combustible storage is characterized by a significant increase in the fire-load and requires approval of the local fire code official. In addition, the code suggests the fire official call for additional engineered fire protection. Potential additional protection measures include fire-proofing of exposed steel columns, increase sprinkler density, in-rack sprinklers, or additional fire department hose connections. These kinds of heights are not usually seen with warehouses that are integrated into a manufacturing facility; however, they would not be exceptional for warehouses providing distribution of finished product.

Conclusion

Warehouses have many common features and yet each one is unique. Understanding inventory and the demand for those materials is crucial to an optimized facility. In addition, to promote life safety and property protection, the code identifies unique measures needed to mitigate the inherent dangers found in these facilities. Warehouses are different from manufacturing and offices and require the appropriate knowledge. When designing or renovating a warehouse, it is important to consult the code and integrate the requirements from the start.

References

1. NFPA, *NFPA 13, Standard for the Installation of Sprinkler Systems* (2019).
2. International Code Council, *2018 International Fire Code: Chapter 32: High-Piled Combustible Storage (2018),* https://codes.iccsafe.org/content/IFC2018/CHAPTER-32-HIGH-PILED-COMBUSTIBLE-STORAGE, accessed 8 Jan. 2019. **PT**

Innovations Maintain the Cold Chain

Amber Lowry

Recent advancements in cold-chain technology offer improved transporting and storing of temperature-sensitive pharmaceutical products.

As focus on the development and manufacture of biologics increases, so does the necessity for competent cold-chain technologies. Over the past several months, manufacturers have released an assortment of products and efforts to preserve the physical integrity of temperature-sensitive pharmaceutical products.

Pallet and parcel shipping systems

Softbox, a provider of temperature-control packaging solutions, released new pallet and parcel shipping systems that include the Tempcell ECO, Tempcell MAX, and Silverpod MAX (1).

The Tempcell ECO is a recyclable parcel shipper made from recycled corrugated paper materials. The ECO uses the company's Thermaflute patent-pending design and is qualified against International Safe Transport Association (ISTA) 7D summer and winter profiles and is able to control different temperature ranges, including 0 °C to 30 °C products.

The Tempcell MAX is a single-use, high-performance phase change materials (PCM) parcel shipper that is qualified to ISTA 7D test profiles and maintains up to 96 hours of thermal protection. The MAX integrates the company's SilverSkin radiant barrier to enhance thermal performance and uses next-generation recyclable Pharmacool MAX PCM coolants.

New to the company's Silverpod pallet shipper range is the Silverpod MAX, a high-performance PCM pallet shipper that incorporates PCM coolants that enable safe storage before and during shipping. The Silverpad MAX also has a SilverSkin reflective radiant barrier for enhanced thermal performance and, like the Tempcell MAX, uses next-generation recyclable Pharmacool MAX PCM coolants.

The previously mentioned shipping solutions were showcased at the IQPC Temperature Controlled Logistics (TCL) conference in London on Jan. 28–31, 2019.

Additionally, the company also pre-launched two temperature control packaging systems at TCL—the AEON Metro and Clinipod—for the delivery of pharmaceutical clinical trials.

AEON Metro is a reusable multi-drop delivery parcel shipper that enables cold-chain delivery without the need for temperature-controlled vehicles. The Metro has reusable PCM coolants that support up to 48 hours of multi-opening thermal protection. The Clinipod is a lightweight carry-home shipper built to facilitate the last-mile delivery of clinical trials to the end patient. Using the company's reusable PCM coolants, it provides up to six hours of thermal protection in extreme temperature conditions.

Poseidon unleashes 'Plug & Play'

Also presented at the 2019 installment of the TCL conference was progress on pharmaceutical ocean-freight network Poseidon's 'Plug & Play' model (2). Poseidon is an industry reform initiative created to improve the conveyance of pharmaceutical products by ocean transport. The initiative includes an independent network of pharmaceutical manufacturers, specialist freight companies, and pharma logistics suppliers joining forces to improve cost, safety, and sustainability of the cold-chain process.

"Poseidon takes the form of a strategic supply network comprising a group of independent pharmaceutical manufacturers in conjunction with all the principal actors involved in transporting a pharma product by sea," said Alan Kennedy, executive director at Poseidon, in a press statement. "Designed from the ground-up, it involves shippers, logistics companies, marine insurers, and product suppliers all being seated around the same table as equal partners."

According to the Poseidon team, state-of-the-art thermal management and real-time shipment visibility are central elements in the Poseidon model, but what sets this initiative apart is its integrated approach, which brings together all

IMAGE: KOKLIANG/SHUTTERSTOCK.COM

cold-chain parties to collaboratively address fundamental problems in pharma logistics. The team also states that in addition to a standard full-container-load operation, Poseidon will be testing a flexible shared-container service in 2019 to cater for smaller consignments and provide maximum flexibility.

Poseidon completed Phase I of a large-scale proof-of-concept pilot project in 2018 and is currently in Phase II. According to the Poseidon team, this field validation project aims to examine cold-chain processes, test-out protective packaging, and verify consignment visibility and data capture and is the largest pharma ocean freight project of its type ever conducted. The project involves the monitoring of several refrigerated container-loads of high-value pharmaceutical products during both summer and winter intercontinental logistics operations, including multiple ocean and overland stages.

Electronic data logger

The LOG-IC 360 Bluetooth Data Logger by American Thermal Instruments (ATI) provides accurate temperature and humidity readings along with safe, secure data retrieval and storage (3).

The data logger allows for remote temperature excursion (thermal alarm) monitoring during product transport. Less than two inches by three inches wide, the device can read individual temperatures up to 300 feet from the unopened product. The lithium coin cell battery has a minimum one-year capacity, a temperature range of -20 °C to 70 °C, and relays data to Android, iOS, or any other Bluetooth-enabled device.

High-precision temperature accuracy is ± 0.25 °C, compared to other industry suppliers at ± 0.50 °C, the company reports. The logger tracks a humidity range of 0–80% relative humidity with communication certifications, which include Federal Communications Commission, Conformité Européenne (CE), and National Institute of Standards and Technology platforms.

Flexible freeze containers

Global materials science company W. L. Gore & Associates has developed GORE STA-PURE Flexible Freeze Containers to protect high-value bulk drug substances from container breakage or leakage during frozen handling, which is typically a vulnerable stage in the product's transport (4).

The containers are constructed of a proprietary high-strength fluoropolymer material that is durable after freezing at -86 °C (-123 °F). In addition to durability, the container's chemically inert, biocompatible, high-purity fluoropolymer composite film has a low extractables profile and offers users the convenience and scalability of a single-use system that efficiently uses freezer space, according to the company.

References

1. Softbox, "Softbox Announces the Launch of New Innovative Temperature Control Packaging Systems," Press Release, Jan. 24, 2019.
2. Poseidon, "Poseidon Exposing its Unique Plug & Play Pharma Ocean-Freight Model in London," Press Release, Jan. 14, 2019.
3. American Thermal Instruments, "ATI Launches Innovative Electronic Data Logger for Cold Chain System," Press Release, Sept. 18, 2018.
4. W. L. Gore & Associates, "Gore to Launch GORE STA-PURE Flexible Freeze Containers at BioProcess International," Press Release, Aug. 21, 2018. **PT**

COVER STORY: DATA ANALYSIS *— contin. from page 18*

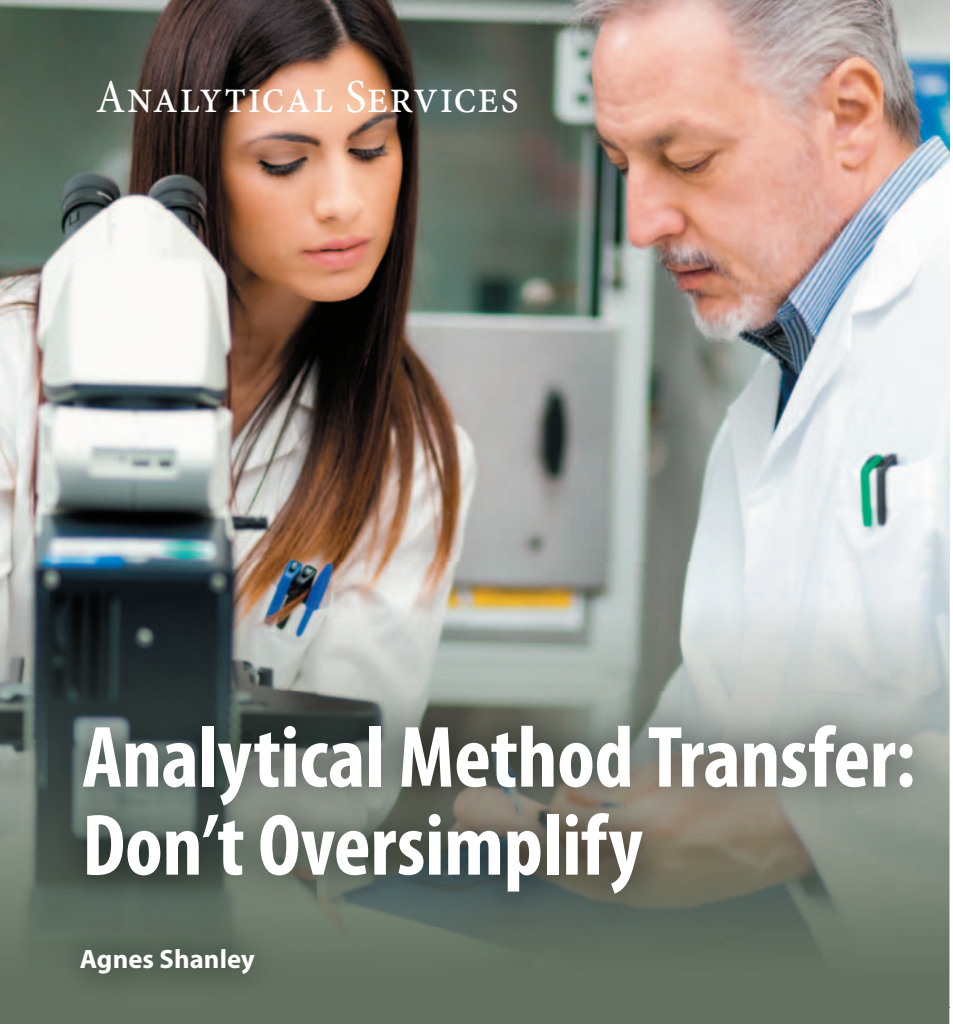
The horizon for software solutions to address pharma customer needs is positive and a fast-moving and competitive space, agrees Manolis. "Broadly speaking, there are many organizations evaluating and using tools that were not designed specifically for pharma but perhaps for business or consumers, and these organizations have been adapting them to their needs. Moving forward, we see these boundaries continuing to blur as solutions are delivered from a variety of software vendors."

Importance of data science experience

Pharmaceutical scientists will need to adapt as well. An understanding of data science is becoming essential. "This experience is key for analytical scientists to understand the data and challenge the data with the right questions and subsequent analyses," Manolis says. "To avoid data silos and facilitate the sharing of data, the expertise gained by the data owner will be invaluable when developing ways to use existing information or to integrate additional data," she adds.

Furthermore, implementing end-to-end data integration requires capabilities that include trusted sources of data and documents, robust quality, and maintenance of data integrity. "The objective is to tackle the most important data first to achieve a rapid return on investment. Identifying the right infrastructure will therefore be of paramount importance," states Manolis. Hovione also believes that data science will allow data-driven predictions from big data through modeling and statistical inference. "Data science will allow the extraction of meaningful information for decision making and consequently allow increased efficiency in pharma laboratories," says Galesio. He does note, however, that many pharma researchers still lack expertise in this field. "Going forward it will be especially relevant to combine both data science and analytical expertise. We believe many companies are investing more and more in this area," Galesio observes.

Many pharma organizations are building structures or have built structures in the past 5–10 years specifically supporting data science and analysis, according to Manolis. "We would assume this investment will continue as modalities and data sets continue to increase in complexity," she concludes. **PT**



Analytical Method Transfer: Don't Oversimplify

Agnes Shanley

When transferring a method from R&D to quality control, success hinges on discovering where "the best" and "the most reliable" intersect.

Analytical method transfer suffers from many of the same problems that plague technology transfer in general. All too often, a method may work well in the R&D lab as a characterization test, but fails when taken to a wider stage, where reproducibility is key.

In addition, incomplete information may be shared between the two organizations working on the transfer, and details on how to carry out standard operating procedures may be given short shrift. Partners may also fail to consider critical points (e.g., whether data interpretation software meets FDA regulations). As Berangere Tissot, general manager with SGS Life Sciences says, "The devil is in the details." Tissot, a subject matter expert on protein and glycoprotein characterization and complex method validations, shared best practices with *Pharmaceutical Technology*.

Conveying the knowhow

PharmTech: What mistakes do people typically make with regard to analytical method transfer for biologics?

Tissot: The most common mistake people make is underestimating the complexity of analytical method transfer, particularly for biologics. The problem that will jeopardize any analytical method transfer, whether at very early or late stages, is the failure to convey the 'knowhow' in documentation that is sent to the transfer partner. Often, instructions are very detailed on some aspects of the method, yet key details are missing because they are not considered critically relevant. It's important to remember that the manipulation of a biologic is very different from that of a small molecule. For some assays, sample preparation is key to the method, and more often than we would like to admit, it is the least described part of the methodology. Even in cases where it is well described, important elements are often missing. This can undermine the difficult challenge of reproducing an assay with consistency and robustness.

Another area where insufficient knowledge transfer typically occurs is when a company has to validate, or ask its contract development and manufacturing organization (CDMO) partner to validate, what was developed as an early phase characterization assay. In many cases, 50 –90% of the information that is needed in order to validate the method is simply not there. Not having the data on hand makes the next step, transferring that method from development to a quality control (QC) environment, a real challenge.

PharmTech: How and what kind of information must be conveyed, and what kind of mindset is needed to ensure that key issues are not left out?

Tissot: Thinking in terms of developing what will later be validated allows one to have more control over the analytical development stage. When you develop an R&D method with the idea that it could be a QC test at some point in the future, you will do it differently than you would develop a characterization test that will remain an R&D characterization test.

When you develop a method that will be transferred to QC or to another lab, you would want to focus on simplifying sample preparation and data acquisition. For example, you would not want to have a 60-step process for sample preparation. You may also consider, whenever possible, how to make the method unbiased to any specific type or brand of instrumentation.

PharmTech: Do R&D scientists have to think like QC technicians?

Tissot: These two categories have different skillsets and mindsets. It does

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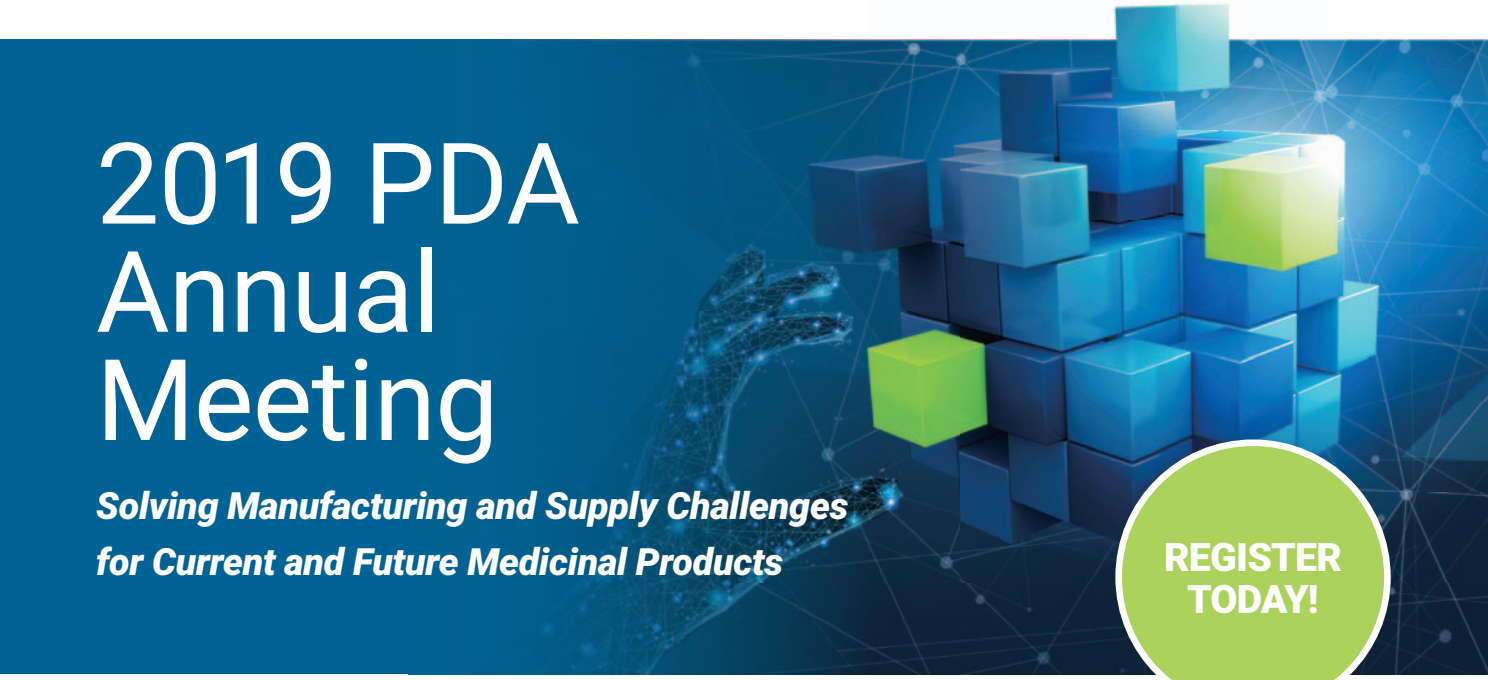

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not mean the two are incompatible, but it requires some training to move from one to the other. When you work in QC, you have to deal with many restrictions on what you can change.

Scientists who are developing analytical methods in R&D typically do not have to consider these restrictions. However, if the method has any chance of ending up on a release panel, they at least need to know what these restrictions are in order to develop an assay that will take them into account.

For example, they shouldn't specify the use of exotic enzymes, however more specific or appropriate they might be for the application. Such materials might pose availability and quality consistency problems that will affect the method's continuity and robustness. For any enzyme that will be used in testing, consistency in quality and multiple sources of supply would be paramount.

Early phase analytical teams are developing a new method because they are looking for new or more precise information. What will work best for moving the method along in R&D, however, is unlikely to work in the QC environment. Thus, it is very important to think about that translation at the beginning of assay development.

We always ask clients, when we are developing methods for them, whether they envision the method being used as a release assay at some point in the future, or whether they see it as having to be validated. Even if no one can be certain at that point, the mere possibility that it might is important for devising the most appropriate strategy around the method development.

PharmTech: But how can one know this at early R&D stages?

Tissot: You don't, at least not with absolute conviction. It is very difficult at that stage. Nevertheless, you may have some sense of whether this approach will be needed, and that sense needs to be communicated to whoever is working on developing the assay so that the method can be built on a solid basis with the appropriate mindset.

This is the major difficulty with transferring analytical methods. Creativity is valued, and imagining the best possible way to approach the method is very important. However, analytical developers must also consider the most reliable way of performing the assay, if it is to be implemented in GMP environments and QC labs later on. Situations will come up where these two goals cannot be matched, and some compromises will be needed.

Managing potential risks

PharmTech: Should these considerations be a part of risk management?

Tissot: It is essential to developing a good risk management strategy around the method itself and its lifecycle. Imagine you are working on the development of a characterization assay for N-glycan structure elucidation that will be used for a drug that has a very complex glycosylation (e.g., for a replacement enzyme, where you know that some form of derivatization or glycosylation will be key to the product's functionality). In this situation, this method, which should normally belong to the characterization panel only, will likely end up being the best approach for monitoring and controlling a critical quality attribute (CQA) of the product.

For the purpose of the characterization assay, you are trying to understand, fully, the complexity of the N-glycan structures. In order to get detailed results, the method might be complex and convoluted. Repeatability or robustness will not be evaluated and rightly so, if this method is just a characterization one. The method efficiency will be as good as the scientist carrying out the assay, which is very common in R&D environment.

However, if you haven't considered the future use of the assay and built some preliminary risk management (e.g., having some specificity, repeatability, and evaluation of the critical parameters to control in the sample preparation) done at the R&D phase, you will need to put a remediation plan in place. Then, a translation phase will need to be developed for that method, to demonstrate that the assay can be brought into QC, and to eliminate most of the risks that could be linked to a complex procedure.

Staffing challenges

PharmTech: Do you need to staff these projects in a special way?

Tissot: I would say that it depends on philosophy and size of the organization. In very small companies, there may not even be a QC or an R&D department. At many of the medium-size pharmaceutical companies, these groups may not be actively working together. However, a growing number of large companies now have groups in between R&D and QC that focus on bridging these two groups and assisting them with the transition of R&D methods in the QC environment. These 'translation' groups generally include people who are educated in QC and understand all the restrictions of QC work, yet who are well versed in R&D, to find that middle ground.

PharmTech: When did you first see this trend?

Tissot: The trend began a few years ago, and it is likely to continue and to grow. Whether that group is involved during the transition or earlier in the analytical method development is a matter of choice for each organization.

PharmTech: You mentioned the importance of describing all steps in detail. Why should that be necessary?

Tissot: This is the key reason why these transfer or transition projects fail. Let me describe one example when we received an R&D method to transfer in our lab and validate to cGMP. The protocol contained many details around the sample preparation, but failed to mention the fact that the protein of interest was adsorbed on plastic surfaces, and therefore was adsorbed on plastic microtubes. It took time to pin the difference observed in recovery to this very basic fact. However, nowhere in the protocol were glass containers mentioned, because it had been so engrained in the mind of the scientists who worked with this protein that 'it went without saying.'

PharmTech: How do you ensure that clients communicate all this information? Do they or you use standardized templates? How do you staff these projects and what backgrounds and experience are needed?

Tissot: We spend a lot of time talking with the client, the scientists who developed the assay, and reviewing the method before we even take the work in. We need to understand each of the steps of the method and evaluate how much of undisclosed details are at each of these steps. It may sound tedious, and we may ask questions that seem unimportant, but all of this is essential to understanding what is critical to the method and what is not.

In general, the more we know upfront, the less we have to ask later. We need to be proactive about the transfer, and clients generally understand that a lot of preliminary work is required in order to maximize the efficiency of the transition and the chance of validating a robust and reliable assay.

PharmTech: Is information technology a factor?

Tissot: Yes, it is a crucial factor. Compliance with US 21 *Code of Federal Register (CFR)* Part 11 requirements is not as critical for R&D methods as it is for cGMP methods.

For some high-end methods, it is still very possible that the software used to analyze data is not yet Part 11 compliant. When such a method needs to be validated, the risk management has also to account for the workarounds to be implemented around the data acquisition and interpretation. This is not trivial and requires close collaboration between the scientific staff, quality assurance, computerized system validation groups, and sometimes, the instrument manufacturer. This consideration must be more apparent to R&D scientists, with the understanding that the method might eventually have to be pushed to the QC lab.

PharmTech: How can both partners minimize risk?

Tissot: Mostly by opening the communication and working around the language barrier between R&D and QC. Our first phase of evaluation is performed on our instrumentation, leveraging our ability to do R&D in a regulated environment. Based on that first evaluation, we define critical checkpoints (i.e., what may pose problem to specificity, repeatability, or any other critical validation requirement) and parameters that may require optimization or adjustments. We also evaluate critical reagents and work our way through defining multiple suppliers to briefly assess robustness, whenever necessary. The method is now in a 'state' where it can be evaluated more in depth for its applicability to release.

What will be investigated next will depend on whether the assay will be used for an identity test, monitoring CQAs, or for quantitative residual testing. Each application will have a set of parameters for which specifications would need to be defined. Based on results, we will either optimize further or go straight to a pre-validation or pre-qualification study to see how the method fares and what could be the targeted acceptance criteria.

Requirements will depend on the clinical phase for which the method needs to be validated. Stringency on acceptance criteria and extent of the study will be different whether the product is in Phase I or III. Once everything has been empirically assessed, we can put a validation protocol in place.

PharmTech: Have you ever had to 'just say no' to a project?

Tissot: It is always difficult to say no because often it's not impossible to work with the method. What can make a project impossible are the requirements that may come with the transfer. For example, when companies want to validate one of their R&D methods, but then ask for it to be validated within a week, they need to understand that this is not likely to be achievable. Rushing to such a critical step in analytical development will likely incur the risk of running into extensive and expensive remediation.

Success requires a lot of homework and careful, educated evaluation of method from a preparation, analytical, and software/IT standpoint. The focus cannot be only on the instrument acquiring the data, but must also include the software analyzing those data and the way the data are being recorded. Everything must be considered.

PharmTech: How can you do the work and comply when the software isn't Part 11 compliant?

Tissot: This requires creativity and a good handle on regulatory requirements, but analytical instrument manufacturers are working on solutions. One can assume that there will be fewer of these gaps in the very near future. **PT**

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Effective Root Cause Determination

Getting to the root of the cause can prevent future problems, says Susan Schniepp, executive vice-president of post-approval pharma and distinguished fellow, Regulatory Compliance Associates.

Q. I am a quality professional in charge of investigations. Sometimes our company has trouble coming up with the root cause for some of our investigations. Can you provide some advice on how to effectively determine root causes for our investigations?

A. You aren't alone in your concerns regarding the inability to identify the root cause when performing an investigation. The regulations for the United States and the European Union require investigations to be performed when deviations occur in the manufacturing process. The ultimate goal of these investigations is to determine why something went wrong, what caused it to go wrong, and how to address the issue and prevent its recurrence. Root-cause analysis is simply a systematic problem-solving approach used for determining the cause of a deviation that occurred during processing and identifying solutions to prevent recurrence.

The following are a few general considerations to keep in mind while conducting investigations:

- One size investigation doesn't fit all situations. Simple errors require simple documentation while more serious deviations require broader investigations.
- The best tool to have is inquisitiveness. Ask yourself how far this deviation could extend.
- Widen your perspective. Look for ways to relate, not separate, similar issues.
- Human error is rarely a sufficient root cause.
- Always verify information or your instincts and never assume you are correct without proper data to support your instincts.

Applying these general rules throughout the investigation should help you get to the true root cause of the deviation.

Once you have recorded the basics of the deviation, you can begin the root-cause analysis portion. Many tools can assist you in this process. Choosing the right root-cause analysis tool is crucial in assuring the process is effective and ensuring the true root cause has been identified. Keep in mind there is no one right tool to use for root cause analysis, and the tool you choose does not need to be complex to achieve its purpose. Some of the available tools include brainstorming, the 5 Whys, flowcharting, and fishbone diagrams. Using some or all of these tools in combination during an investigation is practical and necessary. Most investigation teams start off with the brainstorming technique. This technique is ideal for flushing out theories about the deviation but may not be ideal for compiling the data needed to prove the correct root cause has been identified. Using the 5 Whys or the fishbone diagram in conjunction with brainstorming adds assurance that you have found the true root cause and have gathered the supporting data. Root-cause analysis tools can be detrimental to the outcome of an investigation if they are improperly used, so it is important to train people in their proper use.

The information needed to determine the root cause for any investigation should be appropriately documented. The first piece of information to be recorded should be a thorough and precise description of the event. A timeline that discusses the process up to the time the deviation occurred should be established. Once the event and timeline are properly recorded, a number of questions should be asked and information collected to ferret out the root cause. To make sure the true root cause is identified, each investigation must address the following elements:

- Historical evaluation; have we seen this before on this or other products? Have we seen this before on this line? Have we seen this before with these operators?
- An evaluation of the process/methods used during the operation
- An evaluation of the materials used during the operation
- An evaluation of the equipment/instruments used during the operation
- An evaluation of the personnel involved
- An evaluation of the laboratory analysis associated with the operation
- A review of the validation information for the operation.

Whatever tool/tools you use to identify the root cause of an issue, they need to be supported by a robust, well-documented investigation. Some of the critical elements needed to be addressed in the investigation to support the root cause include a clear, concise description of the issue that delineates what happened, when it happened in the process, and an accounting of who was involved or observed the incident. Other information that should be addressed in the investigation is a record of the immediate action that was taken to minimize or contain the situation.

The investigation should be broad so that all possible causes of the deviation can be captured and evaluated as the possible root cause. Avoid jumping to conclusions and investigate all possible causes so they can be properly eliminated, thus exposing the true root cause. Also, remember that there could be more than one possible root cause to a deviation. If you keep these investigational elements in mind, properly apply your root cause tools, and thoroughly document the investigation, you should have no trouble identifying the true root cause of a deviation and defending it during an inspection. **PT**

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