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Director
Product Development & Supply
Savata, Inc.

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N.D. Ireland

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Professor and Director, Center for Pharmaceutical Innovation and Development
University of South Australia

R. Gary Holloway, PhD
Research Faculty
University of Maryland School of Pharmacy

Ru-yen-ching (Richard) Huang, PhD
Senior Director, Pharmaceutical Sciences
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Colin Minchin, PhD
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Shire Pharmaceuticals

R. Christian Moreton, PhD
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Research Center on Structured Organic Particulate Systems, Dept. of Chemical and Biotechnological Engineering, Rutgers University

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Wendy Safiedi-Glemmer
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The Call for a Rapid Response

Rita Peters

Bio/pharma researchers mobilize to diagnose and treat patients in pandemic threat.

An outbreak of viral pneumonia cases in Wuhan, China at the end of 2019 sparked concerns of another coronavirus (CoV) jumping species from animals to humans, causing a global pandemic. Fears of a repeat of the severe acute respiratory syndrome (SARS) outbreak in 2002 or the Middle East respiratory syndrome (MERS) in 2012 rattled financial markets, led to the lockdown for millions of people, and mobilized R&D efforts around the world.

Chinese officials announced the identification of a novel CoV—2019-nCoV—on Dec. 31, 2019; one month later, the number of confirmed and suspected cases exceeded 10,000, and more than 100 deaths were reported. While nearly all of the cases were in China; other countries, including the United States, had small numbers of suspected or confirmed cases. Authorities in China implemented public health measures, enforcing aggressive travel restrictions and screening programs. Other nations employed screening and travel restrictions.

Meanwhile, the medical research and pharmaceutical communities scrambled to answer basic questions about how the virus is transmitted, stages of contagion, incubation period, and the types—or lack—of symptoms in infected patients. Lessons learned from the SARS and MERS outbreaks are guiding researchers in these efforts.

Following previous outbreaks, the World Health Organization (WHO) placed the SARS-CoV and MERS-CoV on its Priority Pathogen list to encourage the development of countermeasures. Researchers are adapting platform diagnostic modalities used in the previous outbreaks for early recognition and isolation of 2019-nCoV infections and to assess the potential use of broad-spectrum antivirals and vaccines (1). A genomic sequence of 2019-nCoV has been released to public databases, enabling researchers around the world to find clues to detection of the virus and potential treatment options.

The urgency for sharing data and biological material was emphasized in a January 2020 meeting between Tedros Adhanom Ghebreyesus, the director-general of the WHO, and President Xi Jinping of the People’s Republic of China (2). WHO also is launching a clinical data platform where anonymized clinical data can be shared to support the public health response to the outbreak.

FDA Commissioner Stephen M. Hahn said in a statement that the agency is “employing the full range of our public health authorities to facilitate the development and availability of investigational medical products to help address this urgent public health situation.” These efforts include explanations of the development pathways, including Emergency Use Authorization, sharing reference materials for diagnostic development, and directing sponsors of therapeutics to the agency’s Pre-Investigational New Drug Application Consultation Program (3).

Accelerating development
A number of drug companies are investigating the potential for the use of existing therapies as treatment against the virus. Others—backed by the Coalition for Epidemic Preparedness Innovations—are using platform technologies to expedite the development of new treatments. Inovio Pharmaceuticals will use its DNA-based platform development and testing of a coronavirus vaccine matched to the outbreak strain. The University of Queensland in Australia will use its molecular clamp rapid-response technology to develop a new vaccine. And, Moderna will manufacture an mRNA vaccine against 2019-nCoV; the National Institute of Allergy and Infectious Diseases, which collaborated on the vaccine design with Moderna, will conduct investigational new drug and Phase I studies (4).

For an industry accustomed to a slow, methodical development pace, the urgency presented by this health emergency will put R&D skills and resources to the test.

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Pivoting Triple Shaft Mixer

The Ross VMC-1000 VersaMix is a 1000-gallon triple-shaft mixer available on a pivot-design single-post hydraulic lift. The new design allows the machine to be raised from a vessel, rotate 90 degrees, and lowered into another vessel, which allows for convenient discharge of finished product in the first vessel while a new batch is being made in the second. By reducing overall processing time and minimizing downtime, the pivoting mixer saves time and money while simplifying the mixing, discharging, and cleaning operations, according to the company. The mixer is available across a full range of working capacities, from 1 quart to 2000 gallons.

Charles Ross & Son Company
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The Pharmafill NB1, Series II from Deitz is an automated neck bander that can accommodate shrinkbands and full sleeve labels from .79–10 inches in length, giving packaging professionals the ability to apply tamper-evident neck bands to a larger variety of glass and plastic bottles, jars, vials, dropper bottles, metal tins, and other containers in various sizes and shapes on the same neck banding machine.

The stainless-steel device operates at speeds up to 100 bottles per minute and comes equipped with a proprietary touch-screen HMI and a full-access interior for simplified rollstock replacement. The neck bander works with all heat-shrinkable banding materials from 25–123 mm in width applied over caps ranging from 14–76 mm in diameter. Vertical perforators, a photoelectric print registration, a companion heat tunnel, and a conveyor are also available with the device.

Deitz Co.
www.deitzco.com

Biometric Authentication Solution

Werum IT Solutions launched the new K.ME-IN in January 2020, a biometric authentication solution with a wearable Nymi Band device, for its PAS-X Manufacturing Execution System. Users can now authenticate to systems, devices, and machines via a smart wristband.

Each device is assigned to the user based on their biometric identity and can be worn under all types of protective clothing. When authenticated, the device remains on and transmits the user’s identity until it is removed, all while eliminating the traditional method of entering a username, password, PIN code, or scanning a badge.

In the future, Werum plans to incorporate authentication via iris scan, face recognition, and fingerprint into the device.

Werum IT Solutions
www.werum.com

Blister Packaging Machine

The Eagle-Omni blister machine from Maruho Hatsuyo Innovations can be used for packaging development, materials testing and production, and forming, sealing, and punching operations at sequential stations.

The device, which can produce up to 20 blisters per minute, is 1.6 meters tall, has a format area of 150x95 mm, and a forming depth of 30mm or 40mm. It can handle forming materials such as PVC, PVDC, ACLAR, PP, PET, and ALU, and all typical lidding substrates including ALU, paper, PVC, PET, and laminates.

The machine is also capable of manual prototyping and fully automated operation and allows for low-cost prototyping, recipe-driven format change, easy changeover, and various feeding solutions.

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Global Supply Issues Create Challenges

Jill Wechsler

Increased reliance on foreign producers raises concerns and spurs collaborations.

Rising imports of drugs and APIs, at a time when FDA is struggling to inspect and oversee foreign manufacturers, has focused attention on difficulties in ensuring the quality and safety of drugs made overseas. A main FDA strategy is to align with other capable regulatory agencies through agreements to share inspection reports and resources. Ironically, the difficulties in monitoring foreign producers raise questions about efforts by the White House and Congress to boost importation of drugs from Canada to reduce outlays for medicines at home.

FDA’s challenges in overseeing foreign producers were outlined starkly at a hearing before the House Energy & Commerce subcommittee on Oversight & Investigations in early December 2019. This followed a similar session by the panel’s Health subcommittee in October 2019 on the rising volume of APIs entering the United States through a vulnerable supply chain. A main fear is that unreliable and contaminated imports could aggravate shortages of critical drugs and create security risks for the US. The legislators questioned the adequacy of FDA’s foreign drug inspection program, noting ongoing recalls of blood pressure medications manufactured in China and India.

A main fear is that unreliable and contaminated imports could aggravate shortages of critical drugs and create security risks for the US.

In response to concerns raised in a report from on ongoing investigation by the Government Accountability Office (2), Woodcock noted FDA efforts to engage more translators so that FDA inspectors do not have to rely on regulated companies for translation services. A continuing difficulty, she acknowledged, is FDA’s need to announce planned visits to foreign sites to ensure that the facility is operational, while domestic inspections are unannounced. Woodcock noted that limited FDA resources hinder fast resolution of these problems but hoped that a modernized FDA current good manufacturing practice inspection process being implemented would improve the effectiveness of its oversight of all manufacturing facilities.

More collaboration

FDA also looks to reduce the need to inspect certain manufacturing facilities in Europe and other nations through increased participation in Mutual Recognition Agreements (MRAs) with other capable inspectorates. FDA and the European Union finalized an MRA in July 2019 that allows FDA to rely on inspections in EU member states, while European inspectors similarly can request FDA inspection reports on US facilities (3). More recently, FDA announced a new pilot program with the European Medicines Agency and regulators in the United Kingdom, Australia, Canada, and Japan to share information from GMP inspections of sterile human drug manufacturing sites in these and other regions. FDA also is considering additional MRAs for overseeing clinical research sites, test laboratories, and additional products, such as veterinary medicines (4).

In addition, regulatory authorities in all regions are working to improve the effectiveness and quality of GMP inspections through the Pharmaceutical Inspection Co-operation Scheme (PIC/S). Regulators from the US, Europe, Australia, Canada, and other nations have de-
developed recommendations for how inspectors may evaluate a company’s pharmaceutical quality system to encourage more effective manufacturing systems around the world. PIC/S also has published documents to support effective oversight of biological medicines and advanced medical products.

Regulatory programs that encourage manufacturers in all regions to invest in advanced manufacturing technology able to ensure product quality represents the best long-term solution to many of these issues, explained Woodcock at Congressional hearings and in multiple presentations to industry. At December 2019 meetings on global pharmaceutical regulation and risk management sponsored by the International Society of Pharmaceutical Engineers and by the Parenteral Drug Association, Woodcock made the case for establishing a system able to rate US needs. But Florida and several other states have authorized imports will not risk public health and safety in the US—and importer will meet all the requirements for ensuring that such products, as well as offer Glass Delamination studies.

Meanwhile, concerns over high drug prices at home have prompted the Trump Administration to authorize new pathways for states and other entities to import drugs from Canada, and for manufacturers to import their own products made and sold overseas. The rules are complicated and will be subject to extensive comments and revisions; it’s not clear that any potential importer will meet all the requirements for ensuring that such imports will not risk public health and safety in the US—and provide savings for consumers.

It’s also not clear that any manufacturer will seek to sell its own foreign-made drugs in the US at lower prices. And Canadian officials indicate no ability to expand drug supplies to meet US needs. But Florida and several other states have authorized drug importing and are looking for new strategies to do so, despite the potential for further complicating the drug importing picture.

References
Biopharma Analysis
Benefits from New Technology and Methods

Cynthia A. Challener

Analytical solutions are improving for raw material testing, drug product release, process development, and more.

Effective analytical methods are essential for the successful development and commercialization of both small- and large-molecule drug substances and drug products. As the complexity of both biologic and chemical drug substances increases, analytical methods must evolve as well.

“Faster, more efficient techniques will give companies an advantage as their products move through the pipeline,” asserts Robin Spivey, director of analytical research and development, Cambrex High Point. Techniques that are more sensitive and more accurate will, she says, better position a company for regulatory acceptance as long as they are willing to help pioneer the techniques. In addition, such companies will be seen as being at the forefront of the industry.

Some of the most noteworthy advances in analytical methods involve the application of mass spectrometry (MS) for process development and product release of both biologics and synthetic drugs, the enhancement of chromatographic techniques, particularly liquid chromatography (LC), microcrystal electron diffraction, and techniques designed for use as process analytical technology (PAT).

For biopharmaceuticals, MS was initially limited to use for protein characterization to provide supplemental information for regulatory filings, according to Amit Katiyar, director of analytical and formulation development for bioprocess sciences at Thermo Fisher Scientific. Process release/stability testing continues to largely depend on conventional analytical methods such as LC, capillary gel electrophoresis (CGE), imaged capillary isoelectric focusing (iCIEF), and enzyme-linked immunosorbent assays (ELISA) due to their simplicity and wide adoption in quality control (QC) labs.

Inclusion of biosimilars, complex non-monomonal antibody proteins (e.g., fusion proteins), bispecifics, and combination products in the product pipeline, however, is presenting challenges due to the inability to gain a thorough understanding of these molecules using platform methods. “Most of the time, platform methods may not be able to provide the information required to develop and commercialize complex biomolecules. In these cases, MS-based methods are being used for process development and as identity and release/stability indicating methods,” Katiyar observes.

In addition to using peptide-mapping principles in multi-attribute methods (MAMs), major biopharmaceutical companies are now using MS-based identity methods to release biologic drug substances and drug products. “This approach will provide the opportunity
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Chromatographic-based analytical procedures continue to be the most widely used technologies for small-molecule API and drug product analyses and most advances are likely in this area. For the most part, procedures based on high-performance liquid chromatography (LC)/ultra-high-performance LC (HPLC/UHPLC) coupled with ultraviolet detection are most widely used, according to Geoff Carr, director of analytical development in Canada with Thermo Fisher Scientific.

Notable advances in this area, Carr says, include improvements in HPLC/UHPLC column packing chemistries designed to provide better resolution between sample components and greater robustness, such as resistance to particularly high or low pH conditions for mobile phases.

Advances in crystallography are also important for small-molecule API analysis. Microcrystal electron diffraction, also known as micro-ED or cryo-EM, for instance, can be used for structure determination by electron diffraction using micron-sized crystals. “Typically, millimeter-sized single crystals are necessary to achieve unambiguous determination of the absolute structure of an API using single-crystal X-ray crystallography,” explains Heewon Lee, director of analytical research and quality systems in chemical development US for Boehringer Ingelheim Pharmaceuticals.

Micro-ED enables the same level of structure determination using micrometer-sized crystals, eliminating the need to grow larger single crystals, which can be challenging. “This capability is very useful for process development, as understanding impurity formation is a critical step to optimize processes,” Lee says.

Other advances include applications such as near infrared and Raman spectroscopies in support of process analytical technology to enable monitoring of manufacturing processes and the quality of resulting products on-line. “Developments in these areas are in response to regulatory encouragement for the application of quality-by-design approaches for manufacturing drug products,” Carr notes. He adds that this type of technology is more likely to be applied by companies that manufacture their own products and less likely in a contract manufacturing environment.

to gather more information on the performance of MS instruments in QC labs that can then be used for implementing MS technology for process development, release, and stability testing,” says Katiyar. The current approach for regulatory filing, he adds, is to use a combined package of conventional methods and MS methods to gain more confidence from health authorities and be able to present a future case for submissions based only on MS data.

For Da Ren, process development scientific director at Amgen, MAM is probably the most important emerging analytical technology that has been used in process development and release and stability testing of therapeutic proteins. “MAM is an LC/MS-based peptide mapping assay. Unlike profile-based conventional analytical assays, which focus on whole or partial proteins, MAM can identify and quantify protein changes at the amino acid level and can provide more accurate information on product quality related attributes,” he explains. Notably, MAM is capable of replacing four conventional assays including hydrophilic interaction liquid chromatography for glycan profiling, cation exchange chromatography for charge variant analysis, reduced capillary electrophoresis-sodium dodecyl sulfate for clipped variant analysis, and ELISA for protein identification, according to Ren.

In the case of small-molecule drug development and commercialization, MS detection systems are no longer considered just research tools and are becoming more widely used for routine QC testing, for example determining extremely low level impurities such as genotoxic impurities/potential genotoxic impurities, according to Geoff Carr, director of analytical development in Canada with Thermo Fisher Scientific.

“These advances are very likely in response to new regulatory guidelines issued by agencies such as FDA and the European Medicines Agency, but also as a result of specific problems that have occurred in the industry, such as recent concerns regarding observations of N-nitrosamine residues in sartans,” Carr explains.

Efficiency gains for workflows

Changes in analytical workflows have the potential to impact productivity and efficiency but may also create challenges depending on the nature of the modifications. These changes may also originate as the result of new technology or new processes and approaches.

As an example of the former, Heewon Lee, director of analytical research and quality systems in chemical development US for Boehringer Ingelheim Pharmaceuticals, points to material identification using Raman spectroscopy as a technique that has impacted analytical workflows associated with small-molecule API manufacturing. “This technique is now mature, and several companies have launched products that are user-friendly and GMP [good manufacturing practice]-compliant. Benefits are gained because this method can be used to identify raw materials, intermediates, and APIs in the process area. QC personnel can then release batches based on the Raman data acquired, streamlining the analytical workflow,” she explains.

For biologics, using MAM through process development and release and stability testing is a revolutionary analytical workflow, according to Ren. “The continuous monitoring and control of product quality attributes at the amino acid level during product and process characterization as well as release and stability testing enhances the understanding of biotherapeutic products and processes,” he asserts.

One driver leading to changes in analytical workflows is the desire to achieve greater efficiencies and thereby reduce operating costs, according to Carr. One approach that many pharma companies have taken, he notes, is to implement operational excellence initiatives within laboratory operations.

Regulatory pressures for improvements in the scientific understanding and quality of drug product is also leading to an evolution in analytical workflows.
“We are seeing increasing guidelines focused on analytical development, such as a [Brazilian Health Regulatory Agency] ANVISA guideline on conducting forced degradation studies that is very demanding,” Carr observes.

**Automation improves sample prep**

Some of the most important advances in sample preparation tools include increasing application of automation and robotics. Quality-by-design (QbD) approaches to analytical testing can often lead to multiple sampling and testing to achieve a more accurate assessment of the total batch rather than testing one or two samples per batch.

An example given by Carr is stratified sampling for solid oral dosage forms whereby samples are taken at approximately 20 time points during tablet compression or capsule filling and tested for drug content, and three units from each time point are tested. “In circumstances such as this one, there are huge benefits in having automation available in the lab for the preparation of the analytical samples from the 60 individual tablets that require testing,” he explains.

Automation of sample preparation for low throughput methods is also critical to improve turn-around times to support process development activities, adds Katiyar. In general, he notes that automation of all in-process methods for biologics—including size-exclusion chromatography, CE, iCIEF, n-Glycan content and residual host-cell protein, DNA, and Protein A—to support process development activities is crucial for meeting fast-to-first-in-human trials/quick-to-clinic timelines.

In the field of biologics sample preparation, Process Development Scientific Director Jill Crouse-Zeineddini at Amgen sees acoustic droplet ejection for potency assays as an important advance. Acoustic droplet ejection uses acoustic energy instead of tips to transfer a fixed amount of liquid sample from a source to destination plates freely with excellent accuracy and precision, she explains. “The significance of this technology resides in its superb dispensing performance at a very low sample volume. This technology performs direct dilutions instead of serial dilutions and prepares each dose independently, improving assay precision and throughput,” Crouse-Zeineddini observes.

Robust aseptic sampling and automated sample preparation for the purification, desalting, and digestion of protein samples, meanwhile, enables many different product quality analyses. “This technology not only significantly improves operational efficiency, but also eliminates potential contamination and mistakes during manual sampling handling,” states Gang Xue, process development scientific director at Amgen.

Another important point, according to Carr, concerns the reliability of the sample preparation procedure. “This issue is not a new one, but it is becoming more apparent as we apply QbD approaches to our analytical procedures. While the greatest emphasis has been applied to chromatographic parameters, we now realize that the sample preparation stage is at least as important and also needs to be developed using QbD,” he comments.

For Lee, a specific technology development that has improved sample preparation is once again material identification by Raman spectroscopy for small-molecule drug substances. “Using this technique simplifies sample preparation, because it allows identification of compounds without any physical contact with the sample. Depending on the container material, it is even possible to acquire Raman data through the container without the need to withdraw a sample,” she says.

**More developments on the horizon**

Such capability for biologic drug substances has yet to be developed, however, and simplified identity methods to support release and establishing post-shipment identity of bulk drug substance are still required, according to Katiyar. Currently, peptide mapping and binding ELISA are used as identity methods, but they have long turnaround times. Raman spectroscopy has been evaluated for biologics, but it has not yet been adopted by the industry for release of drug substances and drug products. “Simplification using scan-based methods with better specificity and faster turnaround times would be highly beneficial for biopharmaceuticals,” he says.

When integrated with analytical instruments, aseptic sampling and automated sample preparation has the potential to move in-process and product release testing from offline QC labs to the manufacturing floor, either in-line or online, according to Xue. In addition to enabling real-time monitoring of not only cell growth, but also the critical quality attributes of therapeutic proteins themselves, the technology is beneficial for providing much more granular insights into the conventional batch process and products in-flight, he notes.

“More importantly,” Xue states, “it could in the future be crucial for lot definition, process variation detection, and material segregation as required for continuous bioprocessing.”

For small-molecules, Lee would like to see the widespread adoption of x-ray fluorescence (XRF) for metals testing because it would also reduce turnaround times. “XRF is a powerful method for detecting metals used as catalysts in API manufacturing. Compared to inductively coupled plasma-MS, XRF does not require sample dissolution and digestion, facilitating easier sample preparation and faster turnaround times,” she explains.

Carr, meanwhile, expects to see increasing us of LC–MS for routine analytical testing. “This technology is widely applied in chemical drug development labs for various purposes and is also used for biopharmaceutical analytical testing, but less for release testing of products and for testing stability samples. The technology has advanced considerably over recent years, and while these instruments were previously only applied in R&D, they have now become highly suitable for use in routine testing labs,” he remarks.

**Short timelines create challenges**

There are a number of challenges to the adoption of advances in analytical techniques, some of which vary according to the development phase.
Adhering to compressed program timelines is the key challenge in getting advances in method adoption for early stage development, according to Katiyar. “Fast-to-first-in-human (FIH)/quick-to-clinic program timelines have been introduced in almost every pharmaceutical organization to provide clinical material for Phase I studies, and these timelines have shrunk from 18 months to less than 12 months during the past five years,” he says.

The shorter timelines are met by relying on platform approaches developed based on knowledge generated over years with multiple molecules. “For new molecules that fit the platform methods, there is no scientific justification to explore new technologies,” Katiyar states. When working in a lab that is operating in a high-efficiency environment, there is often resistance to the introduction of new methods and approaches due to concerns about meeting delivery targets, agrees Carr.

Once programs move to late-phase development, organizations are hesitant to introduce any change in the control strategy unless it is absolutely needed. This reluctance is particularly strong if a filing has been made to a regulatory agency and/or if significant data have been collected using the older technique, according to Spivey.

“To be adopted for measuring product quality measurement, the performance of new analytical methods must be equivalent to or better than the methods they replace, and there must be clear evidence that they are reliable and robust across a wide range of operating spaces,” states John Harrahy, director of process development in pivotal attribute sciences with Amgen. The adoption of new technology in the middle of a program, adds Katiyar, requires significant effort to develop the new method, perform bridging studies, requalify the method, perform technology transfer (if outsourced), perform retrospective testing, and define new specifications. Bridging studies cost the sponsor additional money and time, and there is always the risk that a bridging study may show that the methods or techniques are not comparable, adds Spivey.

There is also often a reluctance on the part of drug companies to be the first to make a submission to FDA with a new technique due to the possibility of the validity of the technique being questioned, Spivey notes. “They don’t want the burden of having to defend the technique to FDA or other regulatory agencies,” she says. There can be some risk with introducing new technologies that have had limited regulatory exposure, adds Harrahy, particularly considering the different regulatory expectations and change control requirements from different regulatory authorities worldwide.

“With that said,” Harrahy comments, “evaluating innovative technologies is a vital component to ensuring product quality and value to patients, and the ultimate risk of not evaluating new technologies greatly outweighs remaining stagnant.”

The ideal solution, Katiyar argues, is to explore new technologies as part of improvement initiatives without associating them with any programs. This approach provides the flexibility to explore new technologies without putting the program timelines at risk. “Once proof of concept is established and the method is ready to be adopted, a platform approach can be used to implement the new technology,” he comments.

Senior leadership in large organizations, according to Katiya, must provide guidance to their teams to push innovation without risking program timelines.
In addition, it is also important to apply thorough training practices to ensure that scientists really understand the new approaches, says Carr. Continuity of data must also be addressed. “Trend analysis is a widely used tool for monitoring pharmaceutical product quality, and the introduction of new and ‘better’ methods may be perceived to interfere with this trending process,” Carr observes, even though it is more important to apply continuous improvement and accept possible breaks in trends.

**Ways to facilitate adoption**

In addition to evaluating new analytical methods separately from specific drug development programs, there are several other strategies that can be used to facilitate the adoption of advances in analytical techniques.

The best strategy for adopting a new analytical method in a quality setting, according to Harrahy, is to start with the end in mind. Does the proposed method fit the analytical target profile? Is the method sufficiently capable for the product or products that it will measure? Does the methodology require modification to the available GMP/QC environment?

“The robustness, reliability, and value of introducing any new method must be clearly demonstrated, which is often best accomplished by taking a staged approach: determining the method operable design space in a development laboratory, piloting the method in a development/phase-appropriate setting to monitor ‘real-world’ method capability, performing bridging studies vs. the older method, staging its implementation in QC, and continuously monitoring method performance,” he says. In addition, for regulatory acceptance of novel technologies, early partnered engagement with health authorities is strongly recommended, for example, participating in FDA’s emerging technology platform when the new technology has the potential to improve product quality.

The most important strategy, agrees Spivey, is to provide ample data demonstrating that new methods are reliable and robust and that there is little or no risk to implementing the technique in a regulated environment. Advances that offer significant advantage over corresponding currently accepted techniques will also have greater likelihood for acceptance. However, Spivey stresses that the advantage would need to be significant enough to be worth the time and money needed for it to be implemented. "Ideally," she says, "the owner of the technique would perform some preliminary legwork with the regulatory agencies demonstrating the capabilities of the technique. The sponsor would then have some assurance that the agencies would accept their data and make it a less risky approach for them."

Another approach, depending on the nature of the old and new/improved methods, is to run both in parallel for a period of time in order to develop an understanding of how their performance and the resulting data compare, Carr suggests.

For Lee, the key to new analytical method adoption is the sharing of use cases between pharmaceutical companies combined with the publication of white papers and communication with regulatory authorities. Katiyar agrees that sharing knowledge and gaining the feedback of peers and regulatory authorities in a timely manner is essential. "Peer-reviewed publications, conference presentations, and Biophorum Operations Group-like forums are the best places to share information and exchange ideas to improve and adopt new technologies on a global scale," he comments.

**All stakeholders must collaborate**

That information sharing should occur between all stakeholders, including contract research, development and manufacturing organization, testing laboratories, biopharmaceutical companies, regulatory authorities, and instrument/equipment vendors.

"Innovators and service providers need to be open to new ideas and be willing to invest the time and money to implement new techniques. Service providers also, rather than waiting for clients to request a technique before investing in it, should advocate for the use of new methods with their clients," Spivey asserts. In addition, Katiyar believes innovator companies working with service providers should form an external working group to share new methods and technology to eliminate knowledge gaps caused during technology transfer of methods. "Most of the time," he remarks, "innovator companies are not willing to share new methods and technologies and thus delay the adoption of new technologies throughout the pharmaceutical industry."

Regulators also need to be open to new ideas and willing to work with pharmaceutical companies to ensure that new methods and techniques are acceptable for use in a regulated environment, according to Spivey. It is important for pharma companies and regulatory authorities to remember that they have a common goal in identifying new methods and technologies for monitoring and quantifying critical quality attributes that may impact the safety and efficacy of the molecule throughout the lifecycle of the program, adds Katiyar.

He points to MAMs as an example where health authorities have accepted data packages consisting of results obtained using conventional approaches supplemented by those obtained using MS-based approaches.

Instrument/equipment vendors, meanwhile, should be prepared to demonstrate that a new technique is sufficiently better than the currently accepted technique to be worth investing in and worth any potential regulatory risks, asserts Spivey. The dilemma here, according to Carr, is how stakeholders all link together.

"If a new analytical technology comes up, it will not be accepted by industry/regulators unless the equipment that is required to use it becomes widely available. Maintenance, qualification, and repair services must also be widely available and reliable. Typically, however, a vendor will not set establish this level of availability unless there is a level of confidence that sales targets will be achieved. I think that this is the area where conferences, exhibitions, and publications provide a really valuable platform to get the information from innovators and suppliers circulated to end users," he says.
Development

The Search for Transparency in Excipient Sourcing

Cynthia A. Challener

Researching excipient grades and sources, as well as screening suppliers and materials, form the basis of programs to mitigate risk.

Although not pharmacologically active, excipients have a direct impact on the performance of formulated drugs, and their quality and purity are equally important to assuring drug product safety. Because excipients are seldom pure compounds, consistent composition is of utmost importance, asserts Irwin Silverstein, president of IBS Consulting in Quality. Conformance to good manufacturing practices (GMP) is also important so that the customer can rely on the excipient manufacturer’s certificate of analysis (CoA). The wide variety of compounds approved for use as excipients in pharmaceutical formulations, however, creates challenges for sourcing.

Pharmaceutical excipients are typically multifunctional chemistries not exclusively designed and formulated for the pharmaceutical industry. As a result, these molecules often originate from other applications and industries and are later utilized within the pharmaceutical industry, according to Jessica Cansler, a senior quality management specialist with BASF. “The initial manufacturing and quality standards of these molecules were focused more to the requirements of the original application areas and industries, not to the manufacturing and quality requirements of the pharmaceutical industry,” she says.

It is incumbent upon pharmaceutical manufacturers to understand the full excipient supply chain and have in-depth knowledge about selected suppliers. Recognizing that risk cannot be avoided but must be mitigated is equally important.

Many excipient sourcing challenges

The challenges to excipient sourcing vary according to the type of supplier from which the manufacturer is purchasing the material. “Lack of transparency about manufacturing locations and the entire excipient supply chain can provide challenges,” notes Fernanda Onofre, technical service manager for pharma solutions at DuPont Nutrition & Bioscience.

One of the biggest challenges, perhaps, is that many industrial-scale manufacturers make products in multi-application plants, and the volumes produced for the pharmaceutical industry are typically only a fraction of the total production, making it difficult to fulfill pharmaceutical industry expectations (GMP, quality, etc.), according to Cansler.

It can also be challenging to trace back the source of the original materials and understand the quality level of the ingredients, as many are ‘tested up’ to monograph standards rather than produced under the appropriate guidelines, she notes. In some cases, it can be difficult for drug manufacturers to find an appropriate excipient manufacturer fulfilling pharma quality expectations, particularly for legacy products; sometimes drug manufacturers must make compromises and accept what is available on the market.

When the excipient is shipped directly from the excipient manufacturer to the drug manufacturer, there should be no misunderstanding as to the source, according to Silverstein. “However,” he observes, “purchasing through a distributor, broker, or trader may raise a challenge, especially where the excipient has been packaged from bulk or repackaged from discrete packages. Tracing the excipient back to the source relies on having confidence in the packager or repackager and receiving the excipient manufacturer’s certificate of analysis.”

Issues in the past, according to Chris Moreton, principal with FinnBrit Consulting, have related to the sourcing by a distributor of excipients from multiple manufacturers without notifying the customer, which had only validated one source of supply, as well as the switching of plant species from which excipient starting materials have been derived, impacting excipient performance in the manufacture of the finished drug product. Distributors, Moreton says, must inform their customers of the manufacturing sites for every delivery of an excipient.

The pharmaceutical customer must also confirm that the manufacturing site is on their approved list, adds Silverstein.

The excipient manufacturing process can also provide challenges. “This information is often proprietary, yet drug manufacturers need to understand the raw materials and processes that can impart variability in excipients,” Onofre notes. Regardless of the source, therefore, pharmaceutical manufacturers must be willing...
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to invest the time and effort in establishing monitoring systems based on the use of advanced spectroscopic methods, notably for plant-derived excipients, in order to detect unexpected changes in impurity profiles from a single supplier or variations in profiles from different suppliers of the same excipient, according to Moreton. “The difference in levels of concomitant components may impact the performance (manufacture, in-use and/or stability) of the finished pharmaceutical product,” he explains.

Pharma companies should also be sure to conduct supplier qualifications to ascertain the necessary details about excipient suppliers, a process that can provide challenges as well, according to Onofre. “Thorough qualification requires an onsite audit of the excipient supplier, either by the pharma company themselves or by a trusted third party,” she says.

Knowing the supplier is crucial
The first step, Onofre adds, is for pharma companies to fully engage with their excipient suppliers, asking for clarity on the excipient’s entire lifecycle. “Even in the instances where information may be proprietary, much can be clarified after a discussion with the supplier,” she comments. Detailed discussions under a confidential disclosure agreement (CDA) can also help in understanding excipient variability and how that can affect the formulation and process. “Such discussions aid in excipient risk management and the formulation of robust drug products,” Onofre states.

Drug makers should also insist that the manufacturing site of the excipient be identified on each lot of the excipient received at the product manufacturing site, Moreton asserts. The International Pharmaceutical Excipients Council (IPEC) CoA guide (1) establishes that the site of manufacture should be disclosed on this document, according to Silverstein. “Ideally, the batch numbering system of the excipient should be specific, such that a change in the format of the batch number would act as a check for the site of origin,” Moreton adds. Any change in sourcing of the excipient starting material sourcing should also be included as part of the change notification requirements in the quality agreement or in a commercial agreement, with change notification completed per the IPEC significant change guide (2).

On-site audits conducted by the pharma company itself or via a third party, such as EXCiPACT— an international consortium of excipient, chemical, and quality organizations—should be conducted to gather as much information as possible about the supplier and the excipient, Onofre says. If a third-party has been used for the audit, Silverstein adds that it is important to obtain a copy of the audit report to help assure the validity of the audit conclusions concerning production of an excipient in conformance to GMP.

To verify the source of the delivered excipient, whether in the original manufacturer’s container, packaged from bulk, or repackaged, Silverstein comments that the user should verify the authenticity of the excipient label, package, and tamper-evident seal.

Overall, the best approach is to source excipients from excipient manufacturers that clearly commit themselves to the pharmaceutical market and the expectations of the pharmaceutical industry, Cansler asserts. “Usually these excipient manufacturers are appropriately certified to pharmaceutical industry quality standards (e.g., NSF/IPEC/ANSI 363 and or EXCiPACT),” she says.

Pay attention to red flags
When considering different excipient suppliers, there are some warning signs that could indicate potential issues for pharmaceutical manufacturers. For Moreton, a top red flag is not naming the site of manufacture because that precludes physical audits. “Reliance on the distributor’s paper audits or third-party audits for and on behalf of the distributor—and in which the excipient user has no control and is not consulted ahead of time—should not be acceptable,” he says.

The claim that an excipient will meet the United States Pharmacopeia (USP) monograph when tested is a key warning sign for Silverstein. “This language may indicate that the excipient was not produced under ‘appropriate’ GMP as required by USP. Refusal to share non-compendial test methods is another red flag; a good supplier wants to facilitate the proper testing of their excipient, he says.

Pharma manufacturers should also be wary of excipient suppliers that are not aware of current issues, concerns, and trends in the industry they serve, or have to custom-make standard documents, according to Cansler.

Suppliers that are not known in the pharma industry or only have a small presence, as well as those that are unable to provide the required qualification documentation, historical manufacturing trend data under CDA, and support manufacturing location audits raise concerns as well, adds Onofre. Finally, Moreton points to suppliers that are unwilling to enter into quality/change notification agreements as raising red flags.

Be on the lookout for positive attributes
On the flip side, reliable excipient suppliers exhibit a number of recognizable attributes that should be sought. Most importantly, reliable excipient suppliers are open, albeit under confidential disclosure agreements, according to Moreton. They will allow either customer audits or certification to excipient GMP by a recognized accreditation body or certification scheme, adds Silverstein.

These excipient suppliers recognize the importance of the pharma market to their business profitability and participate in appropriate trade associations and meetings. They also have deep knowledge of their products and can provide technical support for their use in drug formulations and provide products with reliable excipient quality, consistent composition, documentation in order, and an established quality management system at the excipient manufacturing site that complies with pharma excipient GMP requirements and expectations, according to Cansler.

“Highly reputable companies in the pharma market, with consistently good performance and proven experience over the years tend to strive for customer satis-
faction and fulfillment through the reliability of their own services and products provided," Onofre concludes.

Selection essentials
In addition to an initial onsite audit, pharma manufacturers should closely evaluate several aspects of excipient supplier performance during the selection process. Identification of the GMPs to which the supplier intends to conform is paramount, according to Silverstein. Standard quality, regulatory, and technical documentation for the excipient should be readily available and complete, coupled with a point of contact to ask questions, Cansler observes. Evidence of the supply chain, quality, and services being offered by the supplier should also be provided, along with in-depth information on the manufacturing locations, notes Onofre.

Access to multiple excipient samples from different campaigns and different raw material lots for qualification is also important, adds Cansler. Excipient suppliers should also sign quality/change notification agreements as part of the overall supply or quality agreement, says Moreton.

Finally, once a supply agreement is in place, Moreton and Silverstein both note that an effective monitoring program at the excipient user site should be implemented to assess the quality and technical characteristics of the excipient.

Excipient grades matter too
Excipient grades are typically differentiated based on a certain physical characteristic (e.g., particle size, molecular weight, degree of substitution, or viscosity). A change in grade means a change in that physical characteristic. For some formulations, a change in grade may not impact product performance, but for others it could be detrimental to the finished product, according to Moreton.

“Different grades allow for flexibility in formulation and process design to address various technical challenges in other raw materials or processes used to manufacture the final dosage form,” Onofre explains. She adds that different grades are also critical for optimizing the right process, which can help in cost-saving efforts in areas from wet granulation to direct compression.

If a specified excipient grade is important to the quality attributes of the drug product, then the formulator should demonstrate in what manner the grade is important, adds Silverstein. “In this case, the homogeneity of the excipient lot for that attribute becomes critical to drug product quality, and the excipient manufacturer should be asked about homogeneity within each lot,” he says. In addition, a change in grade most likely would necessitate a revalidation and a notification under the scale-up and post-approval change (SUPAC) rules, Moreton comments.

Choosing the right excipient grade used to be at the personal preference of the formulator, but with quality by de-
sign widely implemented today, properly designed and executed design of experiments studies give support to the choice of excipient grade, according to Moreton.

In addition to information provided by excipient suppliers, pharma companies may also conduct grade-differentiating testing when establishing excipient specifications. Talking to the excipient technical experts and sharing the intended use for the excipient and the issues to be addressed in the designed formulation can also help in grade selection, according to Onofre. “Based on the API, the formulation, and the intended process, the excipient supplier can recommend the right excipient and the right grades,” she says.

Assuring receipt of the right excipient grade starts at a minimum with identification testing and testing against the CoA/monograph listed tests and parameters, according to Cansler. Services such as infrared scanning flaps/windows in packages, whenever possible, can help reassure the customer about the accuracy of the product and reliability of the supply, adds Onofre.

It is also important to confirm product labeling and product documentation and compare them with the purchase request, Cansler observes. “The excipient specification at the drug maker should clearly link to the excipient supplier’s specification for the grade, and the purchase order should also clearly delineate the grade as it will appear on the excipient package label and CoA,” Silverstein explains. In some cases, he notes that it may also be necessary to discuss with the excipient manufacturer the recommended test method for the parameter that designates the grade and that the accuracy and precision are sufficient to confirm the grade.

As with all excipients, conducting due diligence when approving an excipient supplier and ensuring quality and supply agreements are in place should result in the right product being sent, according to Onofre. Auditing the site of manufacture and the supply chain are important, agrees Moreton. “Testing of the excipient upon receipt at the customer site is often necessary as well because the grade is critical for the particular application, and formulators would be well-advised to test each lot,” he states. Having a sampling plan based on lot homogeneity is also recommended by Silverstein.

Managing risk is the key to success
The most important concept to grasp when dealing with the excipient supply is “Caveat emptor: let the buyer beware!” asserts Moreton. “There are no certainties, and there is always a risk that something may go wrong. However, the risk can be reduced to an acceptable level, but only by acquiring as much knowledge as possible about the excipient and using a combination of site and supply chain auditing, quality/change notification agreements, and an effective monitoring program for all excipient deliveries to the site of use,” he states.

In addition to risks associated with manufacturing processes for excipients, there is risk associated with the distribution and supply chain of excipients globally, notes Cansler. She points to risks associated with the intermediate storage and transportation of excipients. “Trending topics including fraud and adulteration within the supply chain are of serious concern. In addition to raw material qualification, appropriately established supply-chain traceability and supply-chain security processes should be in place,” she observes.

The IPEC excipient qualification guide (3), according to Onofre, provides details on recommendations for building a robust supplier qualification process. “Building customer-supplier relationships that are transparent and provide robust information-sharing opportunities is the foundation for success,” she concludes.

References
In recent years, marketing authorizations of cannabinoid-based pharmaceuticals (namely nabiximols [Sativex] in Europe and plant-derived cannabidiol [Epidiolex] in both Europe and the United States) have been issued globally, although legal and regulatory concerns around cannabis-based products are still apparent (1). As more cannabinoid derivatives are currently in development, there is a drive for developers and formulators to address the challenges these ingredients pose.

To explore the common issues that can be encountered with cannabinoids during formulation and development and the potential solutions that are available to overcome these challenges in more detail, Pharmaceutical Technology spoke with Alyn McNaughton, technical director, Lonza Pharma & Biotech, and David Fulper, director, Technology Support, Softgel and Oral Technologies, Catalent.

**Ingredient challenges**

**PharmTech:** What are the specific challenges facing formulators and developers when approaching cannabinoid-derived products?

**McNaughton (Lonza):** Cannabinoids, generally, have a very low solubility in water and are highly lipophilic. As an example, cannabidiol (CBD) has a solubility of only 0.7 µg/mL (2). Consequently, these materials cannot readily be absorbed orally and, therefore, a large quantity is required to have a medicinal effect. The bioavailability is also significantly affected by dietary fat, which can lead to variability. Alternative routes of administration, such as smoking, present additional challenges, such as potentially producing toxic by-products. These other routes of administration also do not have a significantly better bioavailability and the variability is generally even higher than the oral route.

**Fulper (Catalent):** Stability and first-pass metabolism are probably the two biggest technical challenges. Cannabinoids tend to be oxidatively sensitive, which can be affected by both the formulation and manufacturing process. Tetrahydrocannabinol (THC), and probably CBD, undergo extensive first-pass metabolism, which can be particularly challenging for oral formulations.

An additional challenge is the desire to use extract or “broad spectrum” material that contains multiple components. The variability of these extracts makes it difficult to establish API specifications, develop analytical methods, and even to interpret clinical data. Then there is the political/regulatory challenge for anything related to cannabis, which can often complicate the process.

**Synthetic versus plant**

**PharmTech:** Are there any inherent differences between plant-based cannabinoids or synthesized ones that may impact drug development and formulation?

**Fulper (Catalent):** Molecularly, there are no differences in plant-based cannabinoids and synthetic cannabinoids. As with any raw material supply, there is always the question of purity and related substances, which could differ between the two. The question more often seems to stem from the desire to include other components of plant-based material for a therapeutic effect. The validity of this approach can only be determined through application of adequate science.

**McNaughton (Lonza):** The source, synthesized or extracted, is becoming less relevant to the drug development cycle for cannabinoids as Lipid-based solutions offer a natural approach to improving the solubility of cannabinoid-derived products.
regulators apply pharmaceutical practices. Combinations of different cannabinoids become costly and challenging to get approved due to the permutations of safety and clinical trials required with variations in ratios of these materials required to prove efficacy and safety. From either source, single, pure cannabinoids present the most straightforward route for approval.

While some evidence exists that there are benefits in certain cases for mixtures of cannabinoids, the approval path for this approach is prohibitive and it is likely, at least in the near future, that development of a single, pure cannabinoid will be the preferred route for a pharmaceutical. In other sectors, such as the nutraceutical market, it is likely that some mixtures will still be developed. These mixtures may return to pharmaceutical development areas once the properties of the cannabinoids are more fully characterized individually.

The nature of some cannabinoids to be psychoactive, and consequently by their presence turn any materials into a controlled drug substance, also presents a challenge, mainly for the extracted products. However, extracted materials or those synthesized at a late stage from extracted starting materials still appear to be cheaper than those fully synthesized, at least for the moment, but this is likely to change as the chemistry of synthesis becomes more commonly used.

**Currently available solutions**

**PharmTech:** Could you highlight the currently available solutions that can help formulators overcome the solubility and bioavailability challenges associated with cannabinoids?

**McNaughton (Lonza):** Although other solubility-based bioavailability enhancement approaches, such as solid dispersion, can present some improvement, lipid formulations are the natural approach for molecules with high lipophilicity and low water solubility. Solubility of the cannabinoid in the lipid, and associated excipients, creates an overall solubilized formulation that avoids solid-state limitations for absorption.

**Fulper (Catalent):** Cannabinoids tend to fall into Developability Classification System (DCS) Class IIb (solubility rate-limited absorption), and formulation technologies that improve intrinsic solubility, such as lipid-based systems or solid dispersion systems, may help to address the solubility aspect of poor bioavailability; however, if the compound suffers from high first-pass metabolism overall, bioavailability will remain low. Increasing the dose can sometimes saturate the enzymes involved, but this approach can result in an increase in undesired side effects.

The log P for these compounds tend to be in a range conducive to lymphatic absorption. Using lipid formulations that contain long-chain unsaturated fatty acid components help promote chylomicron production, which are then lymphatically transported into the blood stream and bypass first-pass liver metabolism. The degree to which a specific cannabinoid is incorporated into chylomicrons remains an open and important question.

**Benefits of lipid-based approaches**

**PharmTech:** Why are lipid-based solutions particularly beneficial for cannabinoid-derived products?

**Fulper (Catalent):** Cannabinoids are generally oxidatively unstable. Softgel delivery platforms used to deliver lipid-based formulations are excellent oxygen barriers, and the manufacturing process to make softgels is conducive to protection from exposure to air. Cannabinoids generally have good solubility in triglyceride lipid bases, allowing for easy solubilization in lipid formulations. These formulations, in turn, are readily digested by the body into mixed micelle systems that are readily absorbed into the enterocytes, the intestinal absorptive cells. Cannabinoids can suffer from first-pass liver metabolism. Lipid formulations that promote the formation of chylomicrons offer a path to bypass first-pass liver metabolism.

**McNaughton (Lonza):** Along with the generic potential for lipids to overcome the solid-state limitations for absorption and present the cannabinoids in a solubilized form for intestinal absorption, lipids also present further benefits for highly lipophilic molecules. A secondary contribution to the low bioavailability is the potential for many of these molecules to suffer from first-pass metabolism, where the drug is metabolized, usually by the liver, reducing the quantity reaching systemic circulation. For drugs with a LogD > 4.7 and solubility of >50 mg/g in LCT (long-chain triglycerides) (3), appropriate formulation can promote intestinal lymphatic absorption, over the normal hepatic portal system, undergoing transport directly to the systemic circulation and avoiding first passing through the liver.

**Lipid selection**

**PharmTech:** Could you provide any advice on lipid selection for cannabinoid formulations?

**McNaughton (Lonza):** The selection of excipients comes down to the expertise of the formulator, though there are some general approaches that can be applied. The incorporation of an LCT is preferable, if the cannabinoid is soluble enough in the LCT and the LogD > 4.7. Formulations where LCT, or other triglyceride, is the only excipient are very likely to have large patient and dietary variability. The formulator, therefore, needs to refine the formulation with appropriate excipients, such as surfactants and co-solvents, to allow an emulsion, or preferably a micro-emulsion, to be formed. Ideally, the cannabinoid should also be as soluble in the additional excipients. The closer the formulation is to a micro-emulsion, the less likely it is...
to have patient variability. As well as being able to form and sustain the emulsion through dilution in the gastric system, it is also critical that the solubilization survives the change into the intestinal system and that the digested species of the lipid formulation also continue to solubilize the cannabinoid long enough for absorption to take place.

**Fulper (Catalent):** Lipid selection should always include an assessment of their impact on stability. Many lipids themselves can undergo oxidation. If a less stable lipid is chosen, for instance to target lymphatic absorption, then the source of that lipid should be evaluated for incoming quality. When selecting a lipid to promote lymphatic uptake, long-chain fatty acids are preferred, and unsaturation is preferred to saturated lipids. Solubility should be good in most triglyceride-based excipients. *In-vitro* digestive studies can be used to evaluate the relative ability of the formulation to maintain solubility during digestion.

**Regulatory advantages**

**PharmTech:** Do lipid-based systems provide advantages in terms of time to achieve regulatory approval?

**Fulper (Catalent):** Lipids mimic food and participate in the body’s natural digestive process. In this sense, when you use lipids you are trying to create a food effect (with less calories). In the end, other approaches may work as well or even better, but in my opinion, working within the body’s natural absorption process is a good starting point. Once you have a better picture of the pharmacodynamics involved, you can then decide if another approach might make sense.

From a regulatory perspective, if you plan to produce a generic version of a branded lipid formulation, there may be less concern if you maintain the same or similar formulation approach. Also, [it is helpful that] there is a level of intrinsic abuse deterrent for lipid-based formulations compared to some other delivery platforms.

**McNaughton (Lonza):** From a regulatory standpoint, most bioavailability enhancement technologies are now considered to be well understood and accepted. Generally, any technology that is used to improve bioavailability should aim to minimize the overall quantity of drug substance required and minimize the variability in the patient population. Where the cannabinoid is poorly soluble in water and highly lipophilic, then lipid systems offer the best opportunity to achieve this, making it the most likely approach to be readily approved by the regulators.

**Future trends**

**PharmTech:** What future trends do you predict for solubility and bioavailability enhancement options for cannabinoids?

**McNaughton (Lonza):** More formulations may appear that have been refined to achieve the best bioavailability for each cannabinoid. Beyond this, more synthetic cannabinoid analogues may be produced, either as prodrugs or to modify other properties of the molecule. It is possible that many of these analogues will be derived to promote properties that can be used to enhance bioavailability, which for many is likely to be combined with lipid technologies to maximize efficacy with minimal drug substance. Others may be derived to improve selectivity and efficacy in specific areas, and these may still require significant formulation development to ensure bioavailability.

**Fulper (Catalent):** As the pharmacology of cannabinoids and the endocannabinoid system become better understood, I would expect synthetic cannabinoid derivatives to begin to appear. As part of that process, I think you will see a focus on molecular changes to improve stability and reduce metabolism issues, which are probably the two main challenges with the existing analogues.

**References**


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Designing Commercial-Scale Oligonucleotide Synthesis

Isaiah Cedillo, Bill Jarvis, and Tony Pavone

Consider current large-scale practices as a basis for improving platform strategies.

The strategy of targeting RNA to control processes affecting disease pathology has seen a flurry of clinical success. Regulatory approvals of Spinraza (nusinersen, Biogen), Exondys 51 (eteplirsen, Sarepta Therapeutics), Tegsedi (inotersen, Akcea Therapeutics), and Onpattro (patisiran, Alnylam Pharmaceuticals) in the past few years highlight the relevance of the technology as a new platform for treating disease.

The manufacturing processes being used to produce several of these molecules are built on the solid-phase phosphoramidite approach developed by Beaucage and Caruthers more than 35 years ago. Since then, there has been significant improvement and optimization of the raw and starting materials, reaction parameters, purification, and isolation processes used for oligonucleotides and oligonucleotide mimics. The application of these improvements in large-scale (i.e., multi-kilogram batch) scenarios is becoming more common as more is learned about translating bench-scale methods to a commercial-scale manufacturing setting.

The oligonucleotide field, which is still in its commercial infancy, does not have decades of commercial-scale manufacturing experience on which to draw, but it is beginning to transition to this level of large-scale process experience, as evidenced by drug approvals and new plant capacity. The objective of this article is to provide a framework for developing and improving manufacturing strategies used for oligonucleotides, beginning with an overview of how oligonucleotides are currently synthesized at large-scale.

Some companies internalize their manufacturing capabilities, while others turn to contract manufacturing organizations (CMOs) for process design, scale-up, and implementation. Regardless, the manufacturing facility is most likely to be a multi-product one. There is not yet an oligonucleotide drug requiring significant enough quantities (i.e., metric tons) to warrant a compound-dedicated plant, but most of the companies involved in the manufacturing processes are banking on the success of the oligonucleotide platform to warrant further capital investment. Therefore, the recommendations in this article are directed toward the multiple-product facility where platform processes are paramount for rapid scale-up and minimal compound-specific process research.

Process overview

In its simplest description, oligonucleotide manufacturing consists of only a few, basic unit operations: solid-phase synthesis, purification, and isolation. The earliest syntheses of oligonucleotide drug substance were performed via solid-phase couplings on controlled pore glass (CPG) in sparged bed reactors. While sparged bed reactors are still common and practically useful in high-throughput and small-scale applications, the extensive amount of solvent wash and reagent excess required to accommodate that mixed-bed reactor design are not desirable in larger-scale operations where economic and logistical considerations are important.

Packed bed reactors (PBRs) and higher yielding polymeric, swellable resins (1,2) can accommodate the significant mass addition of a typical oligonucleotide (7 kDa). PBRs are used commonly outside the pharmaceutical industry in chemical applications in which a bed of solid catalyst is interacting with a liquid or gas reactant. Although the phases for oligonucleotide synthesis differ from traditional PBRs (i.e., liquid-solid vs. gas-solid), the same basic design principles apply. Charac-
Regardless of the purification technique employed, oligonucleotide must be isolated from the purification buffer and, in some instances, converted to the appropriate salt form. In nearly all applications, the final isolation step is designed to result in a solid form for logistical, stability, and operational convenience. Ethanol precipitation and ultrafiltration (i.e., diafiltration + concentration) are the intermediate isolation options, and freeze drying is almost always used for the final isolation. In comparison to ultrafiltration, which can accommodate nearly any purification buffer system, ethanol precipitation has limitations on the feedstock solution matrix and oligonucleotide concentration. Therefore, the intermediate isolation operation will be inextricably linked to the method (IEX, RP-HPLC) and mode (step, linear) of chromatography.

Three large-scale processes in-use today are presented in Figure 1. It should be noted that all three leave the final 4,4’-dimethoxytrityl (DMT) protecting group intact at the end of synthesis, which necessitates that it be removed downstream. In the case of Process 1 and Process 3, removal is accomplished via a solution-phase detritylation reaction. In contrast, Process 2 performs the detritylation reaction on the purification column, thus combining the purification and deprotection steps into a single unit operation. The overwhelming amount of large-scale data at the authors’ disposal are from Process 1. Recent large-scale experiences with Process 2 are also presented. While Process 3 is only recently described, its novel use of HIC and delivery of liquid drug substance make it worth noting, although it has not been validated for a commercial process.

Each of the chemistries used in RNA-based therapeutics (e.g., deoxy, 2’-O-methoxyethyl modification [MOE], constrained ethyl [cEt], RNA, morpholinol) present their own challenges, but the basic unit operations used among them are similar. Focusing on oligonucleotides such as those produced from processes presented in Figure 1 nar-
rows the scope of the data but not the basic design principles. Assuming a multi-product oligonucleotide facility producing hundreds of kilograms of drug substance a year is an appropriate, realistic, and useful base case for process design. This article focuses on the solid-phase synthesis step of the manufacturing process, which is the same in all three processes.

**Chemical and analytical considerations**

Solid-phase oligonucleotide synthesis consists of four basic steps: 1) detritylation to remove the 4,4’-dimethoxytrityl (DMT) protecting group, 2) coupling to attach the activated phosphoramidite, 3) sulfurization or oxidation to convert the internucleotide linkage to either a phosphorothioate or phosphate diester, and 4) capping to prevent any unreacted sites from elongating further. At the end of synthesis, cyanoethyl protecting groups are removed from the phosphorus with an amine solution in acetonitrile (MeCN). Support-bound oligonucleotide is then cleaved, and nucleobases are deprotected in aqueous ammonium hydroxide at elevated temperature. Aside from a single commercial product, Ionis exclusively uses the same ion-pair HPLC with ultraviolet (UV) detection coupled to mass spectrometry (IP-HPLC-UV–MS) analytical method for analyzing oligonucleotide. The method utilizes the UV dimension of the analysis for quantifying impurities significantly shorter and longer than the parent molecule and MS for impurities of similar length.

**Large-scale data**

In large-scale synthesis operations at Ionis’ oligonucleotide plant, a variety of process parameters and outputs are tracked as part of production, but the fundamental questions of how much and how pure are most useful for those interested in rugged process design and logistical planning. On average, the UV-pure yield from synthesis is 61%. UV-pure yield refers to the full-length and nearly full-length products (e.g., n-1, where n is the parent molecule). This measure of yield is useful because Ionis’ method of impurity characterization via MS is not ubiquitous, but chromatographic characterization is. Most of the data used to arrive at the 61% average come from 5-10-5 MOE (the 2’-O-methoxyethyl modification) deoxy gapmer compounds, which translates to an average coupling efficiency of 97.56% (0.975620=61%). This is an impressive value considering the near stoichiometric amount of phosphoramidite used in the coupling reaction (1.4 eq.).

The average 5-10-5 compound has a sodium salt molecular weight of 7.7 g/mmol, thus a 100% downstream recovery would translate to an isolated yield of 4.7 g/mmol of synthesis. This value is useful to have in hand for planning purposes. For example, a metric ton of a 5-10-5 would require a minimum of 213 moles of synthesis, but accounting for downstream loss would require more likely 250 moles of synthesis. In approximately the past decade’s worth of data, the yields have been relatively consistent across varying compound motifs and synthesis scales as illustrated in **Figure 2**.

Using Process 1 presented in **Figure 1**, the majority of the early and late eluting impurities are removed in downstream processing, but nearly all of the co-eluting impurities quantified by MS are retained. Thus, the MS impurity profile of the crude is a near-perfect indicator of the drug substance MS impurity profile. The other processes presented in **Figure 1** can afford some modest reduction in co-eluting impurities, but the results at the crude stage will still largely determine the overall MS purity. On average, crudes produced at Ionis have an MS purity of 92%. There has been an upward trend in MS purity over the years (top panel, **Figure 3**) with greater understanding of process-related impurities. The single largest class of impurity contributing to the impurity profile is (n-1), which has also had significant variability over the years (bottom panel, **Figure 3**). This variability will translate directly into the drug substance in Process 1 because these impurities are carried through downstream processing. In theory, Process 2 could have the potential to remove these impurities due to their lower overall charge (i.e., number of charges for interaction with the stationary phase), but in our limited experience...
we have not observed this to be reliably or practically true. Although the author does not have large-scale data for Process 3, one of the recent patent claims is that by careful column loading, HIC can reduce selected \((n-1)\) impurities \((7)\).

In general, Ionis’ practice is to apply platform process experience to new compounds and begin to develop more compound-specific synthesis methods while moving through development into process performance qualification (PPQ). In Figure 4 are data for a single compound where the \(\times\) markers note syntheses where the synthesis process was being varied and the + markers note a fixed, compound-specific method for synthesis. The fixed method was developed based on compound-specific synthesis studies and, as is apparent in the figure, led to less variation in yield and purity.

The data set is considerably smaller, but large-scale results for Process 2 (Figure 1) are similar to Process 1. Unfortunately, the crude analytical method used for Process 2 differs from Process 1, thus making direct comparison difficult. Grossly, the crude purity was slightly higher and the isolated yield slightly lower.

Quantity and quality of material are of paramount importance, but waste and solvent consumption are also worth considering as the demand of oligonucleotide increases. As an example of synthesis solvent consumption, consider four of the syntheses (SYN-000245, 246, 247, 248) that were combined to form a single lot of drug substance. The as-is yield for this lot was 11.488 kg or 4.79 g/mmol. The precise consumption of solvent was totaled and normalized by the lot size in Figure 5. As might be expected, the two largest sources of solvent consumption were toluene and acetonitrile. The consumption, however, only considers solvent consumed during the synthesis and does not include solvent used for cleaning, equipment maintenance, reagent heels, etc. Projecting true consumption requires knowledge of the precise batch sizes, tank volumes, and cleaning procedures. For example, four 10-kg campaigns would likely require more cleaning and reagent preparations than a single 40-kg campaign. As a rough estimation of true solvent consumption across the plant (Process 1), volumes consumed and waste generated are tabulated for Ionis’ plant in Table I. So, although the campaign described in Figure 5 consumed 872 L/kg of acetonitrile during synthesis, the yearly consumption of acetonitrile suggests that 1320 L/kg is a more appropriate value for estimating total plant usage.
Process development

The platform nature of oligonucleotide manufacturing allows for rapid scale-up with minimal process development. The ruggedness of the platform processes being employed is highlighted by consistently high yields and short production times across a range of compounds and chemistries. The average production time from synthesis column packing to unloading the freeze dryer is 67 days, accomplished with a five-day work week and a single shift of engineers. Production times as short as 19 days have been achieved by eliminating intermediate testing, which highlights the efficiency of actual unit operations as opposed to the testing and quality aspects of production.

Prior knowledge and experience have enabled initiation of large-scale, GMP production immediately with little to no laboratory-scale process development. As a compound progresses through clinical development toward commercial production, compound-specific experiments are performed to establish optimal process control set points and proven acceptable ranges (PARs) for PPQ. In establishing these ranges, tight PARs based on historical equipment performance were often used, rather than PARs on what the chemistry could accommodate. Most of the deviations and process failures to date have been associated with equipment failure as opposed to a failure of the chemistry or process parameters. Thus, in choosing a process, simplification by limiting the number of manufacturing steps would be a route to minimizing process failure by reducing the number of potential mechanical failures and equipment errors.

References

Fixed, single-product pharmaceutical factories dedicated to a handful of blockbusters are rapidly becoming a thing of the past. Short timelines, expedited programs, a wide array of increasingly complex therapies, and frequent changeovers between small batches targeting rare diseases place flexible, highly efficient manufacturing plants in high demand.

Today’s drug manufacturers—particularly contract development and manufacturing organizations (CDMOs)—must be agile and adaptable. However, operations in modern, multiproduct facilities are complex and must be carefully laid out and orchestrated for optimal results. This article includes some best practices and considerations for the design and operation of multiproduct pharmaceutical manufacturing facilities.

**Changeovers and cleaning**
In multiproduct facilities, minimizing changeover time between products and zero-defect cleaning are key. Changeover speed is a crucial factor that directly affects capacity utilization, profitability, and timely batch production.

A room or suite clean-out entails washing down and wiping down from ceiling to floor. Therefore, ensure rooms are designed with ready access to all surfaces. Smooth, slick, and sloping surfaces are ideal for quick and easy cleaning. Avoid architectural ledges and grooves. Cabinets should be sloped as well or, better yet, recessed into walls.

Ensure all conduits and piping are contained within the walls. Recess utilities such as electrical, cooling water, compressed air, and steam outlets, or even seal them off when not in use, to eliminate the need for cleaning.

As for equipment, choose automated options such as clean-in-place (CIP). Not only are automated processes more reliable and consistent than manual processes, but their associated documentation is helpful for proving this reliability to regulatory authorities.

Select equipment designed for fast and easy maintenance. Personnel should be able to perform the maintenance routine with the apparatus in place, with minimal teardown. Ideally, one should be able to complete this task during the standard changeover time.

**Cleaning records**
Every cleaning or maintenance process needs a standard operating procedure as well as documentation for every time it is executed. For cleaning automated processing equipment, the record may be an electronic document download. Otherwise, it is often a notation in a tightly controlled logbook associated with that particular device.

Keep careful records for cleaning rooms. In addition to documenting actual cleaning procedures, record all loose items that enter the room on an accountability sheet. Remove every one of these mobile objects for cleaning or disposal elsewhere before stationary equipment is opened. This practice avoids exterior contamination of mobile equipment and prevents contaminants from being introduced into the stationary equipment.

Improper tracking of cleaning supplies can lead to the delayed discovery of unfortunate errors, so always be mindful that equipment is vulnerable when open. This became apparent to one API manufacturer who discovered a cleaning wipe left in a centrifuge charge chute (but not until the first batch after cleaning had been processed), leading to the batch’s rejection. Counting the wipes brought into the processing room and verifying that the same number of wipes were removed would have prevented the loss.

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**Best Practices for Design and Operation of Multiproduct Manufacturing Facilities**

Tim Roach

Careful design, planning, and record keeping are needed for cleaning and changeover.
Cleaning implements and agents
The choice of cleaning implements and agents is important. Sometimes, a simple oversight in this area can compromise a batch. For instance, select only non-shedding sponges and rags to wipe down equipment, or they may leave particles behind.

When changing a cleaning process, always consult the proper stakeholders and documentation to ensure your new procedure is compatible with the equipment. In one case, to achieve cleaning validation, a team switched from a detergent to a solvent-based cleaning solution. Thereafter, in a pre-run inspection, black flakes were discovered around a cover. It turned out that the equipment seals were susceptible to deterioration by the solvent. Fortunately, this problem could be solved by replacing all the seals with a higher-grade material.

Benefits of CIP and WIP
At multiproduct facilities, regulatory inspectors are particularly focused on verifying the adequacy of cleaning and on the prevention of cross-contamination. CIP equipment used for CIP or wash-in-place (WIP) processes goes far to prevent the transfer of material from one batch to the next.

CIP refers to equipment designed so it can be cleaned without being opened. The benefit is speed, convenience, and the avoidance of content being transferred to nearby surfaces or into the air. Such devices have automated cleaning cycles with ports for flushing and require no disassembly. In contrast, non-CIP equipment needs to be torn down with all parts washed separately. This process is extremely time consuming and also raises the possibilities of cross-contamination and operator exposure. As an example, compared with a standard fluid bed dryer, one with well-designed CIP features can reduce changeover times from 12 hours to less than three, with minimal manual breakdown and inspection needed.

One caveat is that, despite the potential benefits of CIP designs, whether a machine can be validated in CIP mode can vary from substance to substance. While some materials are easy to wash away, other materials may be too hard to clean from CIP equipment to pass validation. Similarly, equipment with convoluted surfaces, such as mixers, may be harder to clean. Achieving validation in these situations may require that the CIP equipment be opened and re-cleaned manually as a final step in what is then termed a WIP cleaning process.

While more time-consuming than CIP, WIP is still faster and better at preventing cross-contamination than standard manual cleaning. After the automated cleaning process, it may be just one focal area that needs to be manually cleaned to achieve validation, and the concern of disseminating contaminants has been eliminated by the wash cycle that is run before the machine is opened for its final cleaning step.

HVAC design
Heating, ventilation, and air conditioning (HVAC) design and operation are crucial in multiproduct facilities to control the flow of air and prevent aerosolized products from being disseminated throughout. First, prevent aerosolized materials from leaving production or entry/gowning areas and contaminating the rest of the facility by implementing corridor air-handler systems that maintain air-pressure cascades. To accomplish this goal, always keep corridor air pressure slightly higher than adjacent rooms and airlocks. Equip each production area with a single-pass system that imports 100% outside air. Not only incoming air but also outgoing air must pass through high-efficiency particulate arrestance (HEPA) filters to avoid contaminating ductwork. Replace pre-filters for exiting air with every product change to keep material on the filter from re-entering the room during manufacture of the next product. The right HVAC system not only provides for personnel and product safety but also for the successful operation of a multiproduct manufacturing facility.

Single-use systems
Single-use systems (SUS) may make sense for smaller solid dosage manufacturing batch processes such as material handling and storage (bags instead of bulk containers). The efficiency requirements for research and development, for example, differ from those for large-scale manufacturing. In general, SUS offer the greatest efficiencies at R&D scale, where fewer total batches are required and cleaning methods may not be fully developed, while non-disposable (stainless-steel) components are more practical for commercial-scale manufacturing where cleaning has been validated.

Often in R&D, with a few small batches under 50 kg, no validated cleaning method exists. Time is of the essence, and cleaning validation/verification on a typical weigh-dispense isolator can take 60 to 80 hours between protocol generation, sampling, testing, and review and approval of results. In these cases, SUS are a simple, rapid means of proving equipment is clean. For example, a plas-
tic bag could be used to transport material to a tablet press. The tote would not need to be cleaned, and scoops and other utensils can be disposable. If the batch is under 100 kg, it could even be mixed in a disposable bag.

On the other hand, in commercial solid-dosage operations with many large batches, SUS are generally impractical and not cost-effective. By the time a process has reached this stage, the CMO has usually validated a cleaning method for stainless-steel equipment. Furthermore, large single-use components are costly and would be needed in significant numbers for the many batches being run. In these situations, cleaning validation is worthwhile and stainless-steel components are often the best choice.

**Facility design and operation**

At multiproduct facilities, regulatory inspectors are particularly focused on verifying the adequacy of cleaning and on the prevention of cross-contamination. A facility carefully designed for multiproduct use, with easy-to-clean work areas and equipment as described above, along with appropriate cleaning validation reports, will reassure inspectors. Fundamentally, it must be shown that a cleaning procedure removed all but “an acceptable level” of the product in three out of three tests. Proper good manufacturing practice documentation is essential for approval and traceability. Knowledgeable personnel should be monitoring operations closely to guarantee compliance.

Facilities flexible enough to manufacture multiple products have become a cornerstone of the pharmaceutical industry, crucial for meeting changing market and regulatory expectations. With careful planning, they can be extremely efficient and eliminate the need to build new facilities for every new drug product. Multiproduct manufacturing allows even for drugs needed in small quantities, such as orphan drugs, to be manufactured cost-effectively.

Numerous considerations must factor into the design, equipment, and operation of these facilities, which require more space and different architecture than traditional pharmaceutical manufacturing plants. Overall, these best practices apply:

- Less is more. Design processes with the fewest possible steps to accomplish the task at hand.
- Curtail equipment disassembly as much as possible. Opening equipment introduces risk.
- Minimize the number of items in production rooms; all must be tracked and cleaned.

When investing in pharmaceutical products that can change lives, comprehensive, regulatory-compliant processes must be defined and adhered to for optimal operations in multiproduct facilities. No matter the phase of your project, be diligent to choose a CDMO partner that exceeds your expectations with facilities expertly designed and operated to ensure flexibility, efficiency, safety, and regulatory compliance for your products. PT
Soft gelatin (softgel) capsules can be a means of achieving bioavailability of highly lipophilic drugs that are practically water insoluble. The API is generally dissolved in edible oil. Typical oils used in softgel capsules are medium-chain triglycerides such as Miglyol (IOI Oleochemical) and mono- or di-glycerides such as Capmul (Abitec). For softgel capsules containing lipophilic drugs, the Division of Bioequivalence (DBE), in the Office of Generic Drugs, Center for Drug Evaluation and Research, FDA, will ask applicants to submit a “quantitative rupture” in-vitro drug release test to measure the drug released in the dissolution medium after the capsule shell ruptures (1). The method will typically use a dissolution apparatus 1 (basket) or apparatus 2 (paddle) described in United States Pharmacopeia (USP) <711> Dissolution. In this paper, quantitative rupture testing and dissolution testing will mean the same thing for softgel capsules. Even when the drug is already completely dissolved in the capsule fill, the capsule shell still needs to dissolve for drug release.

A suitable surfactant at an appropriate concentration in the aqueous dissolution medium is a key element for quantitative rupture testing of these softgel formulations. Developing a quantitative rupture test for capsules containing lipophilic drugs formulated in oils presents many challenges. Cross-linking of the capsule shell is the most common challenge. With time, cross-linking will increase, and drug release values may fall below established specifications. Tier 2 release testing with digestive enzymes is an acceptable solution to cross-linking of gelatin capsules (2). During Tier 2 testing of softgel capsules that have cross-linked, an occasional aberrant high value for a capsule may be found. This could be, at times, more than 200% of label claim. This paper discusses what causes cross-linking, how cross-linking is addressed with addition of enzymes, and consideration for occasional high results that can be obtained during release testing.

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Donald A. Johnson
Physicochemical properties of drugs in softgel products

There are two important properties that must be taken into account for getting an oral drug absorbed through the walls of the gastrointestinal tract and into the body: solubility and permeability. If a drug is insoluble in aqueous media, the drug can have very limited bioavailability because there is not a significant driving force for partitioning of the drug from the aqueous environment of the intestinal lumen into the intestinal membrane. On the other hand, if a drug is too soluble in aqueous media, it may not want to partition into the lipid layers of the intestinal membrane. The solubility/permeability trade-off is the basis for the Biopharmaceutics Classification System (BCS) (3).

For drugs that are highly lipophilic, a softgel capsule product can be a useful dosage form for increasing bioavailability of the drug. For the purpose of this paper, the softgel products discussed are those in which the capsule fill contains the drug completely dissolved in oil. The drug will have a high concentration in the oil phase relative to an aqueous medium as indicated by the partition coefficients of the three APIs shown in Table I. Without the oil phase, the concentration of the drug in the aqueous environment of the intestinal lumen is too low to provide a driving force for intestinal membrane permeability.

With softgel products, the drug is already dissolved in the oil fill of the product and drug dissolution is not a physical process that occurs during rupture testing of softgel capsules. Many still refer to release of drug form softgel products as dissolution testing because the quantitative rupture testing generally follows USP <711>. It is the capsule shell that dissolves in order for the drug to be released. Table I shows typical physicochemical properties of three softgel capsule products that have the drug dissolved in an oil fill.

It is seen in Table I that the aqueous solubilities of the three drugs are very low, ranging from nanograms per milliliter to micrograms per milliliter. The solubilities in lipid media relative to their solubilities in aqueous media are high for the three drugs, as indicated by their high partition coefficients, P. The partition coefficient measures the concentration ratio of a drug at equilibrium in a lipid medium and aqueous medium, where the two media are immiscible but in contact. Partition coefficients are commonly determined with octanol and water. In Table I, the partition coefficients show that these drugs have solubility in lipid media that range from approximately 100,000 to more than 10 million times the solubility in aqueous media. Drugs with large partition coefficients would have high permeabilities across the intestinal membrane, thus drug dissolved in an oil fill of a softgel would be an ideal dosage form for drugs with similar properties to those in Table I.

Impact of cross-linking on drug release of softgel products

Gelatin is derived from the partial hydrolysis of collagen. Gelatin crosslinking occurs due to chemical reactions between the peptide chains of gelatin. Once formed in a softgel capsule shell, the capsule shell will only rupture in the presence of proteolytic enzymes if the cross-linking is significant.

Cross-linking is a common problem encountered in the dissolution of gelatin capsules and is most commonly seen during stability testing. Low and incomplete dissolution may be observed while performing in-vitro release testing, as the capsule shell may dissolve slowly and incompletely, delaying full release beyond the specified sampling time point of the test method. If severe cross-linking occurs, bioavailability issues may also arise.

Cross-linking may not occur evenly across a container of drug product. Tables II and III show typical results that may be seen during release testing. In both cases, only one out of six capsules tested has appreciable cross-linking. Table II shows a case where a single low value is obtained. This result is more common in cases where no enzyme is added to the dissolution medium (Tier 1 testing as explained in the following section). In Table III, an aberrant high result is obtained in one capsule. This result is commonly seen in testing with enzymes (Tier 2 testing).

### Table I. Physicochemical properties of APIs in softgel products. MW is molecular weight; P is partition coefficient.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Description</th>
<th>MW (g/mol)</th>
<th>Aqueous Solubility</th>
<th>Log P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paricalcitol (4)</td>
<td>White, crystalline powder</td>
<td>416.646</td>
<td>1.2x10^-6 mg/mL</td>
<td>4.5–7.4</td>
</tr>
<tr>
<td>Dutasteride (5)</td>
<td>Solid</td>
<td>528.539</td>
<td>9.08x10^-4 mg/mL</td>
<td>6.8</td>
</tr>
<tr>
<td>Ergocalciferol (6)</td>
<td>Odorless white crystals</td>
<td>396.659</td>
<td>0.05 mg/mL</td>
<td>7.3–10.44</td>
</tr>
</tbody>
</table>

### Table II. Low result (vessel 6) due to cross-linking.

<table>
<thead>
<tr>
<th>Vessel #</th>
<th>% drug released (45 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
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<td>6</td>
<td>62</td>
</tr>
<tr>
<td>Mean</td>
<td>89</td>
</tr>
<tr>
<td>Min</td>
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</tr>
<tr>
<td>Max</td>
<td>98</td>
</tr>
<tr>
<td>%RSD</td>
<td>15.1</td>
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</tbody>
</table>

### Table III. High result (vessel 3) due to cross-linking.

<table>
<thead>
<tr>
<th>Vessel #</th>
<th>% drug released (45 min)</th>
</tr>
</thead>
<tbody>
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<td>2</td>
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<td>5</td>
<td>97</td>
</tr>
<tr>
<td>6</td>
<td>95</td>
</tr>
<tr>
<td>Mean</td>
<td>108</td>
</tr>
<tr>
<td>Min</td>
<td>92</td>
</tr>
<tr>
<td>Max</td>
<td>163</td>
</tr>
<tr>
<td>%RSD</td>
<td>25.3</td>
</tr>
</tbody>
</table>
Current USP approach to cross-linking
When a softgel product fails dissolution acceptance criteria due to cross-linking, USP allows the use of enzymes in the dissolution medium and allows for two-tier dissolution testing. In Tier 2, pepsin is added to acidic or water dissolution medium to achieve an activity of 750,000 units or less per liter. Pancreatin USP is added to a dissolution medium at or above pH 6.8 to achieve a protease activity of not more than 1750 units per liter.

The two-tier dissolution testing is described in USP <711>. Dissolution criteria for Tier 1 Stage 3 were met at Stage 1. Any result obtained above 125%, for example, would be considered aberrant and may require an investigation.

Physical explanation of aberrant results
When low release values are found in Tier 1 testing due to cross-linking, the addition of enzymes will almost always prove successful in obtaining results within specification. Only with the most severe degree of cross-linking will out-of-specification (OOS) results be obtained in Tier 2 testing. It should be noted, as shown in Table IV, the USP criteria for two-tiered testing does not have upper limits. OOS results are for low release values below the specification limits. Any result obtained above 125%, for example, would be considered aberrant and may require an investigation.

Table V shows actual data obtained in quantitative rupture testing of a pharmaceutical product. The specification for this product is 75% (Q) at 45 minutes. It is seen that the criterion for Tier 1 Stage 3 was not met at Tier 1 Stage 1 because there are release values below 50% (Q-25%). There was no need to continue with stages 2 and 3 of Tier 1 because no additional testing could result in passing Stage 3 criteria. Tier 2 testing resulted in acceptable data at Stage 1.
In Table VI are data from another softgel product on stability after nine months at 25°C/60% relative humidity (RH) conditions. The release specification of the product is 80% (Q) at 45 minutes. The product fails dissolution in Tier 1 testing at Stage 1. Although the product passes the criteria for Tier 2 testing at Stage 1 as shown in Table VI, there are some high aberrant values at the sampling time point of the test method (i.e., 45 minutes). An additional sample was taken at 75 minutes, and the results were acceptable values for the product. The capsules are not super-potent and non-uniform as might be suggested by the 45-minute sample. The high results obtained at 45 minutes are explained by the difference between the time the oil-containing drug is released from the ruptured capsule and the time the oil droplets are taken up by the surfactant micelles.

Surfactants form micelles when added to the dissolution media above their critical micelle concentration. Micelles are spherical in shape and have diameters on the order of 10–50 nanometers. During rupture testing, an oil droplet emerging from the capsule shell will have a diameter on the order of 0.25–0.5 millimeters. A micelle with a diameter of 30 nm has a volume of 1.4 x 10^-20 mm³. An oil droplet with a diameter of 0.25 mm has a volume of 8.2 x 10^-3 mm³. The volume of the oil droplet is on the order of a quadrillion times that of the micelle volume. However, there are many micelles capable of taking up all the oil released from the capsule. The oil in a typical softgel fill will be from 250–350 mg. The amount of surfactant added to the dissolution medium is on the order of 10s of grams.

Table VII shows examples of dissolution methods for softgel capsules.

When an oil droplet is released from the capsule, there is a finite amount of time it takes for the tiny micelles to take up the large oil droplets. If the time when an oil droplet is released from the capsule shell is too close to the sampling time, the drug distribution in the dissolution medium may not be homogeneous because the oil droplets have not been fully taken up and absorbed by the micelles. In this case, sample taken may include an oil droplet not yet taken up by the micelles, resulting in high aberrant results.

As an example, say the sample volume is 1 mL and the dissolution medium is 1000 mL. If a drug product contains 2 mg of API in 250 mg of oil fill, the even distribution of drug at full release in the dissolution medium would be 2 µg/mL. But, if an oil droplet containing the drug has not been fully taken up by the micelles because the time between capsule rupture and sample time is insufficient, high release results will be obtained if any small oil droplet is included in the sample volume. Two mg of API in a 250 mg of capsule fill is 8 mg/mL. This means a droplet size of only 0.25 µL taken up during sampling will contain 2 µg of drug result in

### Table V. Tier 1 failure at Tier 1 Stage 1 with specification met at Tier 2 Stage 1.

<table>
<thead>
<tr>
<th>Vessel #</th>
<th>Tier 1 Stage 1</th>
<th>Tier 2 Stage 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11</td>
<td>101</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>101</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>103</td>
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<tr>
<td>4</td>
<td>71</td>
<td>113</td>
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<td>5</td>
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<td>104</td>
</tr>
<tr>
<td>6</td>
<td>108</td>
<td>105</td>
</tr>
<tr>
<td>Mean</td>
<td>49</td>
<td>104</td>
</tr>
<tr>
<td>%RSD</td>
<td>78.7</td>
<td>4.1</td>
</tr>
<tr>
<td>Min</td>
<td>11</td>
<td>101</td>
</tr>
<tr>
<td>Max</td>
<td>108</td>
<td>113</td>
</tr>
</tbody>
</table>

### Table VI. Aberrant high values at Tier 2 testing.

<table>
<thead>
<tr>
<th>Vessel #</th>
<th>45 min</th>
<th>45 min.</th>
<th>75 min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80</td>
<td>121</td>
<td>98</td>
</tr>
<tr>
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<td>66</td>
<td>165</td>
<td>115</td>
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<tr>
<td>3</td>
<td>34</td>
<td>152</td>
<td>108</td>
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<td>4</td>
<td>35</td>
<td>120</td>
<td>99</td>
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<tr>
<td>5</td>
<td>18</td>
<td>133</td>
<td>101</td>
</tr>
<tr>
<td>6</td>
<td>36</td>
<td>122</td>
<td>100</td>
</tr>
<tr>
<td>Average</td>
<td>45</td>
<td>136</td>
<td>104</td>
</tr>
<tr>
<td>RSD</td>
<td>52</td>
<td>14</td>
<td>6.4</td>
</tr>
<tr>
<td>Max</td>
<td>80</td>
<td>165</td>
<td>115</td>
</tr>
<tr>
<td>Min</td>
<td>18</td>
<td>120</td>
<td>98</td>
</tr>
</tbody>
</table>

### Table VII. Examples of dissolution methods for softgel capsules (7). USP is United States Pharmacopeia. Source: FDA.

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Dosage form</th>
<th>USP apparatus</th>
<th>Speed (RPMs)</th>
<th>Medium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paricalcitol</td>
<td>Capsule</td>
<td>I (Basket)</td>
<td>100</td>
<td>4 mg/mL (0.4%) lauryldimethylamine N-oxide (LDAO)</td>
</tr>
<tr>
<td>Ergocalciferol</td>
<td>Capsule</td>
<td>II (Paddle)</td>
<td>100</td>
<td>0.5 N sodium hydroxide (NaOH) with 10% Triton-X-100 (polyethylene glycol tertocylphenyl ether, Sigma Aldrich)</td>
</tr>
<tr>
<td>Dutasteride</td>
<td>Capsule (Soft-Gelatin)</td>
<td>II (Paddle)</td>
<td>50</td>
<td>Tier I: 0.1 N hydrochloric acid (HCl) with 2% (w/v) sodium dodecyl sulfate (SDS) (900 mL) Tier II: 0.1 N HCl with pepsin (as per USP) (450 mL) for the first 25 minutes, followed by addition of 0.1 N HCl with SDS (4% w/v) (450 mL) for the remainder of the dissolution test.</td>
</tr>
</tbody>
</table>
a drug release of approximately 200% label claim. A 0.25% droplet in a 1 mL sample size would be hard to visually detect in the sample.

Conclusion
Dissolution testing of softgel capsules is better described as quantitative rupture testing because the drug is already dissolved in the oil fill of the drug product. The critical dissolution that occurs in quantitative rupture testing of softgel products is dissolution of the capsule gelatin shell. When cross-linking of the gelatin shell occurs, release of the drug from the capsule will be retarded. The impact of cross-linking on bioavailability is not significant if it can be shown that the drug release is overcome by addition of enzymes to the dissolution medium. If during Tier 2 release testing, drug release is below specifications, cross-linking is most likely severe enough to affect bioavailability. If, on the other hand, aberrant high dissolution results are obtained, the high results are indicative of release of drug from the capsule at a rupture time that is close to the sample time. Subsequent sampling beyond the sample time of the test method will result in assay values more in line with the product label claim.

It is important to understand results obtained from quantitative rupture testing of softgel capsules. Aberrant high values during quantitative rupture testing should not be interpreted as super-potent drug product or non-uniformity of dosage units. However, aberrant high results may still require careful consideration and possibly a laboratory investigation. Low results obtained during Tier 2 testing with enzymes may signal a possible problem with *in vivo* bioavailability. Experience with quantitative rupture testing is especially important during stability testing in understanding the performance of the drug product.

References
7. FDA, Dissolution Methods, Database, *FDA.gov*. PT

Donald A. Johnson, PhD, RAC is senior scientific advisor at Eurofins BioPharma Product Testing.
Advances in protein engineering have empowered pharmaceutical developers to optimize and exploit the therapeutic potential of proteins much more quickly and cost effectively than usual, while maintaining or even enhancing their safety profile (1). Innovative recombinant protein therapeutics, such as monoclonal antibodies (mAbs), fusion proteins, and antibody-drug conjugates, are now being used to treat an expanding range of conditions, including cancers, inflammatory, autoimmune, and genetic diseases. Structurally larger in size than small-molecule drugs and functionally dependent on post-translational modifications (PTMs), these classes of therapeutics bring added complexity to the protein characterization process.

With greater protein complexity comes the need for robust analytical methods. Current analytical technologies, workflows, and data processing methods need to accommodate the requirements for biotherapeutic protein characterization (i.e., confirming identity and detecting PTM status for each residue, and measuring abundance of both major and minor intact protein isoforms to ensure the quality and consistency of these products). Such a thorough characterization effort would not only help protect patients for whom the drug will be developed, but also reduce the time required to bring these protein-based therapeutics to market. A robust, reproducible characterization protocol also functions as a quality control step to measure batch-to-batch variability of the drugs. As with all high-throughput fields, giving researchers the ability to automate time-consuming steps will make the characterization process even more productive.

This article considers the challenges associated with determining the structure of complex protein biotherapeutics, and how researchers can employ the latest mass spectrometry (MS) technologies and workflows to confidently characterize these increasingly important drugs in an efficient and comprehensive manner.

The challenge of complex protein therapeutics

Recombinant protein therapeutics are intricate molecules, typically orders of magnitude larger in size than traditional small-molecule drugs. The production of these biotherapeutics relies on living cells or organisms that are extremely sensitive to a range of factors, such as species origin and culture conditions (1). As therapeutic efficacy often requires preservation of precise secondary or tertiary molecular structures, comprehensive characterization is required during development and manufacture. Gaining such structural insights can be difficult when synthesis is complicated—often requiring over 5000 critical process steps to generate a recombinant biotherapeutic (2).

Given the need to assure the safety and quality of these therapeutic products, there is a growing requirement for reliable analytical methods capable of quickly characterizing the structure of these molecules. There is also a need for these methods to reduce the number of test strategies required and the potential for operator error. Moreover, with the growing number of hybrid therapeutic products under development, such as...
antibodies fused to highly glycosylated or otherwise analytically challenging molecules, the technologies and workflows used by researchers to confirm the structure of these complex molecules must keep pace with the evolving biopharmaceutical landscape.

Comprehensive protein characterization typically involves a combination of intact mass analysis and peptide mapping to confirm both the total mass of the species and elucidate the substructure in fine detail. Ongoing improvements to the capabilities of high-resolution accurate mass (HRAM) analyzers and complementary dissociation techniques, as well as increasingly reliable and efficient protein digestion solutions, have enabled highly effective peptide mapping workflows that can probe protein structure at the individual amino acid level. Additionally, recent advances in MS technology are now enabling powerful non-denaturing liquid chromatography–mass spectrometry (LC–MS) methods for intact mass analysis, reducing the reliance on orthogonal, non-LC–MS-based approaches. These so-called “native” LC–MS strategies are enabling researchers to support the characterization of microheterogeneous isoform mixtures of covalently assembled molecules. The combined analysis directly correlates identified features to each proteoform, removing the need for manual inferences.

Traditionally, denatured, intact mass analysis generates convoluted MS spectra containing a mix of intact mass isoforms and wide charge state envelopes with much greater charge state overlap, which result in the production of complex mass spectra. Although spectral deconvolution algorithms can be used to interpret this complexity, these computational workarounds have their limitations. Performing MS in non-denaturing conditions, a characteristic feature of native MS, can help mitigate these issues. By spraying the intact protein sample in physiologically approximate buffers consisting of volatile salts, native MS enables the protein to retain its native structural characteristics and, in effect, shield internal basic residues from becoming protonated in a typical positive mode MS analysis. Folded protein isoforms have decreased charge states and increased spectral separation between each of the isoforms in a mixture, resulting in relatively simplified mass spectra. With native MS, it is often possible to achieve the resolution of intact protein isoforms, such as mAb glycoforms, without the need for sample pre-treatment.

Newly developed data processing tools, used in conjunction with state-of-the-art MS systems, enable accurate interpretation of results.

Coupling native MS with separation techniques that are compatible with “native” mobile phases, such as size-exclusion chromatography (SEC), provides a convenient and automated analytical workflow that can effectively resolve the complex protein architecture. As a result, native SEC–MS intact mass analysis can deliver cleaner spectra and provide reliable characterization data in a high-throughput fashion.

Advanced MS tools for intact mass protein characterization

To characterize complex proteins in their intact state, in addition to optimizing the native MS methods, significant efforts are made towards charge reduction techniques with the goal of obtaining improved resolution. In recent years, advances in SEC–MS intact mass analysis have been driven by the advent of solution-phase charge reduction additives, such as triethylammonium acetate (TEAA). Due to the high pKa values associated with these additives, these reagents enable protons to be efficiently abstracted from the protein, reducing the overall charge (z) on the analyte. The lower value of z imparted by the additives shifts the mass-to-charge ratio (m/z) distribution, resulting in higher m/z ratios and better spectral separation. Higher concentrations of additive can facilitate enhanced charge reduction and improve the spectral separation of intact protein isoforms. However, a frequent challenge encountered when working with solution-phase additives is the need to regularly clean heated capillaries because the build-up of material can quickly have a detrimental impact on analytical performance.

Proton transfer charge reduction (PTCR), an alternative technology using gas phase ion source reagents, can help overcome the challenges posed by solution-phase additives. The ion–ion proton transfer reactions serve as an effective method for gas-phase charge reduction, yielding cleaner spectra while minimizing maintenance requirements. Recently, PTCR has become commercially available, providing researchers with wider access to this technology in a vendor-supported format. For example, an advanced ion source and modified dual-pressure linear ion trap (e.g., such as that only available in the latest Thermo Scientific Orbitrap Tribrid mass spectrometer) provides significantly increased ion–ion reaction efficiency, which provides support for enhanced PTCR capabilities. Through the application of other proprietary innovative ion management technologies, including hardware that more precisely manages electrical fields and reduces noise, these designs can maximize ion transmission from injection to detection, delivering robust qualitative and quantitative performance. Such improvements can eliminate electrospray ionization (ESI) source contamination and simplify the MSn spectra of intact proteins and complexes, ultimately increasing confidence with intact and top-down protein sequencing.
Advanced workflows

**MS instrumentation.** The use of PTCR as a powerful strategy for intact mass analysis has been further facilitated by the extended high-mass-range functionality offered by some modern instruments. The latest Orbitrap Tribrid system, for example, is now capable of performing high mass measurement and isolation up to 8000 m/z, enabling the higher-order analysis of large-protein complexes and their components. Moreover, this next-generation system is capable of supporting both peptide mapping and intact mass workflows in a single platform. Fragmentation techniques with higher energy collisional dissociation (HCD) and electron transfer dissociation (ETD) facilitate more detailed peptide mapping, while automated PTCR-enabled charge reduction applied to native MS yields improved resolution for intact mass analysis. Using ion trap isolation to further isolate smaller m/z windows helps significantly improve the signal-to-noise ratio, allowing for more control in the experimental workflow to characterize complex biotherapeutics. Native MS coupled with sequential enzymatic dissection of individual subunits in highly glycosylated proteins, such as etanercept, can offer additional information on glycan heterogeneity compared to bottom-up peptide mapping, thereby acting as a fingerprinting tool to assess batch-to-batch variability of drugs (3).

The features of this advanced MS instrument help scientists obtain the high-quality protein characterization data necessary to drive the right decisions along with the ability to expand their experimental capabilities in the future.

**Data acquisition.** Further advances in MS technologies and workflows are helping researchers confidently characterize protein therapeutics more quickly. The latest intelligence-driven data acquisition strategies, such as charge state directed dissociation, are delivering improved analytical specificity and making data collection significantly faster. By enabling spectra to be processed using automated precursor determination, precursor charge state analysis can be performed in real-time, enabling the intelligent selection of the dissociation techniques to be employed as well as the optimal parameter settings for high-quality MS acquisition. For example, higher charge state precursors may fragment significantly better using a combination of ETD and higher-energy collisional dissociation (EThcD), requiring both the duration of ion–ion reactions and relevant collisional activation energy to be imparted. Intelligent MS methods have been further extended utilizing data-independent acquisition PTCR to be implemented following ETD spectral acquisition. These workflows can boost efficiency and accelerate the generation of high-quality results through more complete MS’ spectral acquisition and confident, automated data processing.

**Data processing.** Newly developed data processing tools, used in conjunction with state-of-the-art MS systems, enable accurate interpretation of results. For example, the Sliding Window algorithm (Thermo Scientific BioPharma Finder software) used for deconvolution of intact proteins “slides” along a chromatogram, acting as an overlay to generate time-integrated results (4). Traditional intact protein deconvolution involved averaging all the spectra corresponding to an arbitrarily selected chromatographic time. However, with numerous LC peaks eluting over time, averaging all the spectra in a selected time doesn’t accurately represent the protein isoforms present in separation. By interrogating smaller windows within a larger chromatographic range, modern software algorithms perform deconvolution multiple times in succession, resulting in a more accurate understanding of how the spectra behave and change over time. As the set window width increases along the LC time axis, different isoforms in the chromatographic separations can be detected multiple times. Redundant detections improve the confidence of reported isoforms, in terms of both mass and abundance. Using the minimal percentage offset enables the greatest number of redundant detections, thus allowing the detection of even minor components that may elute for shorter times. Applying these approaches to characterize biotherapeutic proteins allows researchers to analyze mass spectra of different protein isoforms with varied elution profiles. Performing deconvolution using the Sliding Window algorithm can, for example, provide more accurate drug-to-antibody (DAR) ratios, taking even the lower abundance species into account when analyzing antibody-drug conjugates.

The future of protein characterization

A few years ago, analyzing an intact complex protein sample would have yielded a mass spectrum that would pose significant deconvolution challenges, making it difficult to be analyzed or interpreted. The latest MS systems, with the capacity for native analysis and charge reduction with PTCR, have opened up the possibility of comprehensive and automatable characterization of highly complex proteins in a single platform. However, with the ability to isolate every portion of the spectrum and closely examine the charge state distributions of the isoforms present, researchers must take care not to introduce implicit bias to their analysis. The application of the latest technologies can eliminate the risk of a skewed isoform distribution, especially when characterizing therapeutic proteins, relieving the possibility of introducing any bias.

The nature of protein therapeutics will continue to evolve as the field of protein engineering accelerates. Simultaneous advances in MS technology will ensure researchers have access to analytical tools that can keep up with the increasing complexity of modern biotherapeutic products.

**References**

Data Management Practices

Lauren Lavelle

Data management is crucial in bio/pharmaceutical laboratory settings from discovery steps through clinical studies and varies based on the development phase.

In nonclinical settings, good laboratory practices (GLPs) ensure the quality of the studies conducted, including the integrity of the data collected. Features needed for compliant data management include detailed final study reports, the proper storing of all raw data, documentation, and protocols, and a responsible archivist to maintain responsibility for the stored data (1).

Development and manufacturing laboratory operations, such as quality control, have additional/different data requirements. Good lab practices rely on a study director as a single point of contact for all open-ended studies on product performance for submission to FDA for pre-market approval. As the study is being conducted, a quality assurance unit inspects each phase to oversee the integrity of the studies and compliance or non-compliance with the GLPs and records them in an index. In contrast, good manufacturing practices (GMPs) don’t require a single point of contact and depend on a quality control unit to approve and reject certain methods and procedures to determine whether products and samples meet manufacturing requirements (2).

Bio/pharma laboratories have access to a range of services and tools designed for accurate and quick data sharing via data backup and mining and configuration tools. An additional software system intended for lab data management is an electronic lab notebook (ELN). Intended for documenting research, ELNs manage and store lab research data while allowing for collaboration between members of a lab group or outside resources contributing to the lab work (4). Most platforms are also accompanied by content creation tools, workflow suitability, and integration tools for connecting to other software or online services.

The latest version of the Matrix Gemini LIMS from Autoscribe Informatics works to provide a range of labs with proper business and operational needs through configurable workflows (5). The system can mirror lab workflows and Matrix configuration tools while leaving the underlying code unchanged, making it easier for labs to upgrade product versions. It also allows users to download the specific configurations of their system and send them to the Autoscribe support team for assistance.

“LIMS investments are typically for a five to 10-year period, often longer. A truly configurable solution makes it simpler to meet changing business requirements, as well as adopt new processes, instruments, and systems as the lab evolves. This ‘future proofs’ your investment and ensures a lower cost of ownership over...”
the lifetime of the LIMS,” said Tim Daniels, marketing manager for Autoscribe, in a press release. “A truly configurable LIMS provides every laboratory the certainty of longevity without sacrificing the flexibility to adopt the new technology and integration being driven by current Laboratory 4.0 initiatives.”

LabWare’s ELN is a paperless solution for the testing of GMP samples alongside standard operating procedures (SOPs) and standard test methods by quality control labs (6). The notebook can be incorporated into Labware’s LIMS to offer access to quality data, product specifications and control limits, training certifications, instrument calibrations, and standard or solution data.

The software also includes a compliance view that monitors the statuses of the methods as quality control analysts complete each step. Supervisors are notified when adverse events occur in the lab so problems can be corrected immediately.

NuGenesis Lab Management System from Waters Corporation uses synergistic data, workflow, and sample management capabilities to track product lifecycle from discovery to manufacturing (7). The system is equipped to link data such as sample submission and results review, stability testing, scientific search, multi-vendor software connection, laboratory inventories, data retention and legal hold, and laboratory execution methods to the businesses it is providing for. It can also adapt to different informatics environments and enable software integration and standardization without long deployment times.

Garrett Mullen, senior product marketing manager, Laboratory Management Informatics at Waters Corporation, said the NuGenesis Lab Management System is comprehensive and can readily adapt to informatics environments to easily link data from the lab to the business operations of a company so the organizations can see and know more about the lab processes (8).

Agilent’s SLIMS can manage all lab data through a web browser or cloud host so individual labs can tailor it to their own LIMS preferences. The system features sample management, an ELN, and workflow management capabilities (9).

Additionally, the system provides complete transparency for any lab sample, a workflow solution combined with protocols and external analysis platforms, an ELN module for digital note-taking and follow-up of experiments, and a sequencing tool kit.

The most recent version of the platform, SLIMS 6.4, provides an authentication module for account creation, additional analytical workflows, and instrument calibration for equipment expiration date tracking and to provide consequences for protocol steps (10).

BIOVIA’s LIMS is purpose-built to maintain the necessities of the lab management process. The system requires no custom coding and uses its own internal system administrator to organize applications, workflows, and procedures, eliminating the need for external consultants and programmers (11).

It also features automatic workflow validation that produces a complete validation document for the application, workflow, or procedure, and a fast deployment time that reduces the validation time from months to weeks.

Also from BIOVIA is the BIOVIA Inventory, a web-based platform for lab materials, equipment, supplies, and reagents mangement that can be used as a standalone or with an ELN (12).

The program works to lessen lab inventory and supply spoilage, restrict the opening and preparation of new materials when supply is already available, prevent the use of expired products, and oversee controlled and radio-labeled substances.

SampleManager LIMS software from Thermo Fisher Scientific can readily adapt to various lab methods and processes while working in conjunction with several software systems including enterprise research planning and manufacturing execution system software (13). The system also allows for portability through a mobile app, which gives analysts the opportunity to use the system anywhere in the lab. The app uses tablet cameras and barcode scanners to scan samples and locations and lets users directly upload methods, SOPs, and results.

References
1. FDA, Code of Federal Regulations, Title 21, fda.gov, April 1, 2019.

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References
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Managing Risk for Cell and Gene Therapy Logistics

Agnes Shanley

Vein-to-vein programs are focusing on data access and traceability.

The past few years have seen dramatic growth in cell and gene therapy research and commercialization. As questions of access and cost continue to come up, developers are adding new capacity to help keep up with explosive demand for new therapies. Over the past few months, Kite Pharma and Novartis have both built new facilities in the United States and Europe, while Lonza, WuXi Biologics, and other contract development and manufacturing organizations (CDMOs) have been expanding manufacturing capacity.

Established ways of gathering, transferring, and storing data and materials for traditional biopharmaceuticals will not work in the evolving supply chain for autologous and allogeneic therapies. For one thing, manufacturing and transport involve many more diverse stakeholders and patient groups than traditional programs, while, for autologous therapies, there is a need to closely coordinate raw material extraction and final product production, and transport to and from collection centers and from manufacturing to clinic.

Over the past six months, alliances have started up to streamline data management and access to improve the transmission of data from raw material collection points to manufacturing, and to patients at the point of use. In one such collaboration, the CDMO Lonza, IT company Vineti, and logistics specialist Cryoport are working to optimize logistics for cell and gene therapies.

Lonza’s formal collaboration with Vineti had begun in July 2019, to integrate the CDMO’s MES and electronic batch record (EBR) execution solution with Vineti’s supply chain orchestration platform, designed to connect manufacturers and healthcare providers at point of care, in real time.

Vineti, which focuses on supply chain management for cell and gene therapies, has been in business for approximately four years, and grew out of GE Ventures, says cofounder and CEO Amy DuRoss. Back around 2012, a leading biopharmaceutical company with a chimeric antigen receptor T cell (CAR-T) product in Phase III had approached GE to help with unprecedented manufacturing and supply-chain issues. The product, which is now commercially available, was being produced almost entirely manually, says DuRoss, and presented the most complex supply chain and logistics workflow requirements ever seen in the history of biologics. “They were using brute force against the production and delivery of each therapeutic. Once they saw that they were likely to commercialize, they realized that there was no way to scale production and delivery on a manual basis,” she says.

For roughly two years, GE Ventures evaluated the challenges involved, and Vineti was set up in 2015 as an independent company to automate those specific supply chain and logistic workflow requirements. The company uses an enterprise platform developed inhouse, and an integration layer driven by application programming interfaces (APIs).

Simplifying data integration
With CDMOs, the connection point depends on what the partner wishes to emphasize. With Lonza, for example, the emphasis is on the MES and EBR system. “Vineti is managing chain of identity and chain of custody externally, and providing data as a feed internally into Lonza’s shop floor,” DuRoss says.

The two partners plan a number of other integration efforts that will deepen the capacity for data sharing and integration to improve capacity optimization. “CDMO customers no longer have to handle data integrations themselves, since the system will already be built for them to link into,” she says. Cryoport’s Chief Commercial Officer Mark Sawicki discussed its
to make the process move faster and more smoothly, but, as an industry, we aren’t there yet.

Finally, the manufactured materials themselves are extremely fragile and irreplaceable, but they have to be pushed back out under very rigorous timelines and exacting conditions. You don’t have the latitude for deviations because they might destroy the product or even kill the patient. All of these elements create significant complexity that the industry hasn’t had to deal with before.

**Data management and IT systems**

**PharmTech:** What do these challenges mean for CDMO and sponsor data management and IT systems?

**Sawicki:** IT is a huge consideration. We are now working to integrate our individual IT systems so that information flows from one system to the next. The goal is to eliminate the need for manual intervention and reduce the risk of human error. At Cryoport, we have also begun to use artificial intelligence (AI)-based tools to examine product workflow, the risk elements associated with moving material in, manufacturing, and moving product back out. The only way that these AI systems can be effective is by gaining access to large amounts of data, and we’re now able to pull that data through our partnerships.

**A potential role for AI**

**PharmTech:** What is required for inter-connectivity, and did you develop the AI systems in-house or with a partner?

**Sawicki:** Systems must be nimble enough to talk to each other, so that if there is a delay during one phase of the process (e.g., during transportation, manufacturing, or administration) the information can be pushed out through the entire system so that everyone understands the ramifications of what is going on.

We hired our own data scientists to develop the AI systems, although Vinetti is working on AI systems of its own. Our use of AI is focusing on all around risk management for materials, and how we can use existing data more effectively to manage risk and improve operations, whether for storage or distribution. By the third quarter of next year, we expect to roll out a new version of our software that will include several of the AI features that we’re working on now.

**PharmTech:** How do you connect to CDMOs and to the clinical side? What elements are needed?

**Sawicki:** We typically connect through electronic data interchange or APIs using either a pull or push, bidirectional, or unidirectional process from conduits that have been designed to transition or share data with clients’ enterprise resource planning systems and portals, as well as Vineti’s IT platform. In some cases,

**With cell and gene therapies, full traceability is crucial because any deviations from prescribed transportation conditions can destroy product.**

elements of our IT system are being replicated inside a partner’s site.

If a Lonza client, for example, wants to schedule distribution of an autologous product, they can go into Lonza’s system, find an interface to our system, and get whatever help they need. Solutions providers such as Vineti are designing systems that are as flexible as possible to enable data to flow more easily between systems.

**Specialized containers and cleaning validation**

**PharmTech:** What led Cryoport to develop the customized containers?

work in cell and gene therapy logistics and supply chain management with Lonza and Vineti with *Pharmaceutical Technology*.

**Scheduling can be very challenging, especially for autologous materials.**

**Tackling challenges**

**PharmTech:** What is one of the most challenging aspects of working in cell- and gene-therapy logistics today?

**Sawicki:** The supply chain is far more complex than it is for monoclonal antibodies or small molecules. Regenerative medicines are patient-specific materials. You cannot simply order bulk materials and manufacture lots of product and just push those out to market. In addition, there is a lot of variability in procuring the materials (i.e., you’re typically dealing with severely immunocompromised patients, so scheduling to get them in to pull materials, to transport or manufacture them, can be an issue). In some cases, patients can get sick or there can be weather issues.

As a result, scheduling is extremely challenging, especially for autologous materials. It is a bit easier for allogenics, but, at this point, networks for transporting donor materials have not yet been fully vetted.

Complicating the picture is the fact that the manufacturing processes associated with autologous therapies are not mature. This means that developers often have to extend instrumentation and processes that have been used for single-patient production to large-scale manufacturing in a commercial manufacturing environment. The interconnectivity and optimization of workflow isn’t there yet. Companies such as Lonza are trying to identify automation competencies
Sawicki: The advanced therapy shipper line is a segregated, specially engineered fleet to support the distribution of clinical and commercial cell and gene products. We rolled it out to get ahead of what we anticipate future FDA regulations to look like, and to focus on what we expect to become most important feature of any shipment and packaging product in this space: traceability.

Currently, two third-party foundations, the Foundation for the Accreditation of Cell Therapies and the Standards Coordinating Body for the Alliance for Regenerative Medicine, are putting together recommendations for FDA in conjunction with ISO [International Organization for Standardization] TC 276, which will establish a long-term regulatory framework for the cell and gene space.

Our goal is to use the same standards that you would see in a GMP manufacturing environment for the equipment that is used to transport these materials to end users. Some standards are data related (e.g., for data loggers, track and trace, and geo-fencing), but the most important aspect is establishing traceability for equipment performance.

We can verify and confirm the historical utilization of every piece of equipment, who used it, and where and for what. That’s one of the most important elements that is being introduced in the program.

We’re also introducing a validated cleaning process for the industry that demonstrates a 99.9999% reduction in all contaminants, which brings it as close to product sterilization as possible (since it would be physically impossible to sterilize shippers and tanks out in the field). This will eliminate the risk of cross-contamination.

Sawicki: Existing standards are based around International Safe Transit Association (ISTA) protocols that have been used for the past 30 years. One liability is that these protocols incorporate a tolerance for deviation that is fine for small molecules or many biologics but could potentially render regenerative medicines unuseable.

With many cell and gene therapies, deviations from prescribed environmental conditions, even those that last for a few milliseconds, half a second, or a second, can destroy product completely. There is no visible way to tell whether the cells are still useable after an upset. You won’t be able to tell if the viability of the cells has gone from 90% to 10% without doing extensive testing.

This is why full traceability is so important, so that you know how a given piece of packaging will perform each time it leaves or returns to the manufacturing facility. Traceability looks at the risk of cross contamination, at equipment performance, and at the traceability of each shipment and whether it has been subjected to any shocks or condition deviations.

These data will eventually be connected to outcomes research. Say, for example, a sample has been shipped at the correct temperature, but affected by shear events along the way. It will eventually be possible to determine whether these incidents had any impact on product efficacy. If a client has dosed 13,000 patients during this time period, they would be able to examine the data and see any patterns that come up. We maintain every bit of data generated by our systems and can currently go back nine years and provide regulators with any information they request.

Services bottleneck
PharmTech: Is there currently a bottleneck in the services available for cell and gene therapy development?

Sawicki: As more products come to market, there are issues with scale. Some producers haven’t had the bandwidth to keep up with demand, and this has held back their growth. Then there is the issue of viral vector manufacturing capacity and the risk of having a single supplier for the required materials.

Currently, many of the materials required for GMP manufacturing of cell and gene therapies are single sourced, which is extremely risky, and manufacturers are typically smaller providers because this is a niche industry. The 800-pound gorillas aren’t yet supplying reagents and other necessities because there was no market for them five years ago. However, today there is still a pipeline of 1000 clinical products, all of which use GMP starting materials from single, small provider sources. That poses a major risk.

Scaleability issues
PharmTech: How about scaleability?

Sawicki: This is easier to manage for autologous treatments. As you move to allogeneic products, instead of 2000 or 3000, you will be dealing with two or three million, and fleets will move from 1000 to 100,000. There’s only so much existing capacity for liquid nitrogen shippers. This is also true for storage and distribution. For example, how will pharmacies do the visual inspection required when releasing allogeneic product from a liquid nitrogen tank when performing visual inspection can potentially render product unuseable? The industry must resolve many of these questions.
In sterile manufacturing and aseptic fill/finish of pharmaceutical products, isolator technology offers the ability to achieve high sterility levels. PharmTech spoke with two experts to learn about best practices in specifying and operating isolators. Richard Denk is senior consultant for Aseptic Processing & Containment at SKAN AG, which designs and manufactures isolators, isolator process solutions, and cleanroom equipment. Denk founded the Parenteral Drug Association (PDA) Isolator Expert Group, which has published guidelines for isolator design and cleaning. Denk was also responsible for writing about transfer systems and isolator design for PDA's technical report on isolators, which will be published in 2020, and is chair of the International Society for Pharmaceutical Engineering Germany/Austria/Switzerland (ISPE D/A/CH) Affiliate’s Containment Expert Group, which published the ISPE Containment Manual. Steve Nole is vice-president of operations at Grand River Aseptic Manufacturing (GRAM), a contract development and manufacturing organization (CDMO) for parenteral pharmaceuticals. GRAM is building a new aseptic processing facility, near its existing facility in Grand Rapids, Michigan, that uses isolator technology from SKAN. The company is currently in the process of equipment qualification, with good manufacturing practice (GMP) production planned for start-up in September 2020.

**Isolators vs. RABS**

**PharmTech:** What do you see as the advantages of isolator technology for aseptic manufacturing? When are isolators a good choice compared to restricted access barrier systems (RABS)?

**Nole (GRAM):** The main advantage for isolator-based technology is that it removes the most significant source of contamination from the aseptic environment by eliminating direct interventions by gowned employees. Typically, with an isolator system, a higher sterility assurance level (SAL) is achieved. Also, isolators can be placed in a Grade C surround, which requires less cleanroom real estate, whereas RABS require a higher level of air classification and additional airlocks, more stringent gowning requirements, and support to operate and maintain a Grade A/B RABS system.

Both isolators and well-designed RABS systems can achieve very high SAL. Isolators may be a better choice for a new greenfield building because you can achieve a higher SAL, operate in a Grade C space, and recognize lower operating expenses due to a smaller cleanroom and less gowning requirements; however, isolators require a higher initial investment for equipment costs. RABS may be best suited for upgrading existing equipment already within a Grade A cleanroom. Lastly, a company may choose RABS/isolator lines based on the company’s existing technology and training. For example, a company with existing RABS lines may stay with RABS for consistency and training of the workforce.

**Denk (SKAN):** Isolators most comply with the regulatory requirements of the pharmaceutical authorities, such as FDA or the European Medicines Agency, with regard to sterile manufacture. If you look at the Draft Annex 1, which was published in December 2017, you will find the term ‘isolator’ 34 times throughout the document (1). Draft Annex 1 is a European document, but [global regulatory] members, such as FDA, WHO [World Health Organization], and PIC/S [Pharmaceutical Inspection Cooperation Scheme] are in-
volved in this document, which also makes the document of international importance. The advantage of isolators is the barrier between the operator in production and the sterile product to be manufactured. The operator is seen as the highest contamination risk to the sterile pharmaceutical product. Compared to the RABS, which is decontaminated together with the room, the isolator has its integrated decontamination system, which offers significant advantages. As a result, the aseptic area involved in this document, which also is becoming increasingly important. The advantage of isolators is the barrier between the operator and equipment vendors worked together in the past, how many installations they have fully commissioned in the United States, and support and service capabilities. These factors become even more critical if the OEM (original equipment manufacturer) is responsible for routine maintenance and requalification activities.

**Denk (SKAN):** In the fill/finish area of sterile manufacturing, isolators are primarily selected and specified to ensure an aseptic environment in the filling process. In addition, if the pharmaceutical product is a highly active or highly hazardous substance, there are additional protective factors on the isolator to secure the operators during production. The topic of cleaning to avoid cross-contamination in a multi-purpose system is becoming increasingly important. The permitted daily exposure (PDE)/acceptable daily exposure (ADE) levels are getting lower; especially in the fill/finish area, any external contamination in the vial or syringe, for example, can quickly exceed the PDE/ADE. In order to prevent this, I founded a PDA expert group in 2015 that has now published two PDA publications on the subject of cleaning and avoiding cross-contamination. The first publication, *Isolator Surfaces and Contamination Risk to Personnel and Patient*, deals with the limit values for cleaning of non-direct product contact surfaces inside and outside of isolators with the associated equipment such as the filling line (2). In the second publication, *Preventing Cross Contamination During Lyophilization*, cleaning and its limit values for surfaces not in contact with the product within a lyophilizer were considered (3).

In addition to these factors for the selection and specification of isolators, other factors such as the surrounding equipment also play an important role. How do the stoppers and caps get into the isolator? Or if ready-to-use (RTU) primary packaging, such as nested vials or syringes, are used, how are they introduced and the packaging removed?

**Best practices**

**PharmTech:** What are some ways to address challenges for moving material in and out of the system?

**Denk (SKAN):** Transfers in and out of an isolator are areas that should be examined closely in a risk assessment, because they have an impact on sterility and containment. The risk assessment should be performed in the beginning (during mock-up) and include GMP and EH&S [environment health and safety] requirements. Different decision criteria play an important role in the selection of the suitable transfer system. Is the intention for a large-scale pro-

**“Best practices [include] a multi-product risk assessment to determine risk mitigation practices.”**

—Steve Nole, GRAM

**Specifying isolators**

**PharmTech:** What are some of the keys in choosing/specifying isolators and surrounding equipment?

**Nole (GRAM):** Factors to consider include decontamination cycle time, changeover, residual vaporized hydrogen peroxide after decontamination, and where/how the vaporized hydro-

**Operations**

“The topic of cleaning to avoid cross-contamination in a multi-purpose system is becoming increasingly important.”

—Richard Denk, SKAN
Nole (GRAM): You need to have a robust system in place that provides flexibility. GRAM can use a combination of dedicated parts that are autoclaved and transferred into the isolator via rapid-transfer canisters, or preassembled and gamma-irradiated assemblies in bag-in-bag-out with rapid-transfer ports. This setup allows us to assemble and sterilize our own assemblies or source preassembled material from a third party.

PharmTech: What are best practices for cleaning/decontamination of isolators?

Nole (GRAM): All removable size parts and dedicated parts are removed and cleaned per batch. Any materials that can be autoclaved (bowls, hoppers, tracks) are autoclaved and set in place with a plastic (Tyvek) cover in place. Once the line is set up, the isolator and all materials inside undergo a decontamination cycle with vaporized hydrogen peroxide. For multi-product filling lines, best practices are to have a multi-product risk assessment to determine risk mitigation practices, and to create a program for routine monitoring of the cleaning efficiency.

Denk (SKAN): The new Draft Annex 1 describes that the surfaces should be validated as cleaned before they are disinfected or decontaminated. In my opinion, complex surfaces as well as a multitude of flexible connections, inaccessible areas, etc. are difficult to clean and to validate. I have been dealing with the subject of cleaning and hygiene design of surfaces for many years. In order to be able to clean processes in a reproducible and valid manner in the future, the technical implementation has to be rethought to reduce the components that are installed within an isolator to a minimum and then make them easily accessible for cleaning. Building on the hygienic design, surface decontamination in the isolator is then carried out using evaporated or sprayed hydrogen peroxide. When it comes to surface decontamination, I am a big supporter of integrated systems in the isolator, since the technology is in line with the process and isolator design, and the hydrogen peroxide is brought to the surface to be decontaminated as quickly as possible. There are two different systems here: evaporation of the hydrogen peroxide by means of an evaporator plate and distribution in the isolator chamber by means of recirculation. Another possibility is the direct spraying of the hydrogen peroxide with a two-component nozzle, using SKANFOG technology. With this nozzle, the liquid hydrogen peroxide and compressed air are mixed and micro-droplets are generated. These micro-droplets are distributed at a high speed in the isolator and, due to the fast atomization, form a uniform film on all surfaces, resulting in short decontamination times of a few minutes.

PharmTech: What are some of the best practices for maintenance of isolator technology?

Denk (SKAN): The best practice for maintenance of isolators is predictive maintenance. The isolator is the aseptic barrier between the sterile product and the environment. The better this barrier works, the safer the sterile product. Some maintenance personnel are particularly distinguished in keeping the isolators in good shape for a very long time. I’m often surprised seeing isolators installed many years back that still look like new. We have a SKAN Academy where all of our service people are trained, as well as the operators of our customers if they have no experience with isolators or would like to enlarge their skills. Most of our customers have a service contract and are thus informed about their upcoming maintenance to be coordinated with their production cycle.

Nole (GRAM): Most OEMs offer routine preventive maintenance and decontamination-cycle requalification packages until a company has in-house expertise. Finally, one crucial best maintenance practice is a glove maintenance/management program. Understand your glove change frequency and have six to 12 months of inventory on the shelf—gloves have long lead times.

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Successful drug development depends on work done before clinical trials begin. As innovators outsource more of their discovery and pre-clinical research (Sidebar, p. 55), contract research organizations (CROs) are taking over more early development activities. Their involvement typically begins by helping sponsors determine the best target therapies to pursue, after which pre-clinical in-vitro and in-vivo testing evaluate the toxicity and optimal dosage of these therapies.

Outsourcing is the only way for virtual companies and charities without internal resources (i.e., hospitals and institutes developing therapies for rare diseases) to develop their own pipelines, with projects set up so that sponsors can tap into and manage multidisciplinary teams. But even for larger companies with internal R&D assets, outsourcing has become a way to improve capital efficiency and elasticity, and reduce overall cycle times, says Vicky Steadman, general manager of Eurofins Integrated Discovery. Her division focuses on identifying the best drug candidates for pre-clinical studies, which are then carried out by other divisions of Eurofins.

Companies have already reduced cycle times, but abbreviated regulatory approval pathways have made it even more challenging to balance the need for speed with the mandate to meet FDA’s current good laboratory practices (CGLPs) requirements. Illustrating what can go wrong at the pre-clinical research phase, in October 2019, FDA issued a warning letter to Novartis’ subsidiary AveXis, citing problems with data from early animal studies for its new therapy, Zolgensma, a treatment for the rare disease spinal muscular atrophy (1). The company had only alerted regulators to problems with the data after the drug was approved. In addition, regulators found other CGLP issues at the lab, including unexplained discrepancies in potency assays, incomplete records, and failure to follow testing protocols or quality assurance procedures.

Paralleling CGMP problems found in recent FDA warning letters for manufacturing, recent CGLP citations for pre-clinical testing often emphasize lack of root cause analysis and corrective action, and failure to follow testing protocols and standard operating procedures (2).

Compliance with CGLPs
One of the most important aspects of any pre-clinical collaboration between a sponsor and CRO is ensuring that work meets CGLPs and other regulatory requirements. That is not necessarily difficult, but can be more challenging than it sounds, says Nancy Catricks, executive director of regulatory compliance at the CRO, Charles River Laboratories. The fundamental requirement is establishing appropriate quality systems at the testing facility, she says.

Nonclinical safety studies are legally required to be conducted according to CGLP regulations if they support or are intended to support applications for research or marketing permits for products regulated by FDA, she says. “CGLPs were enacted to assure the quality and integrity of study data and reduce the chances of unreliability and fraud. Following these regulations appropriately assures that studies are reliable and allows FDA to make sound decisions for patient safety.”

Ensuring data integrity remains a key challenge, as shown by the AveXis warning letter, and many CROs have established formal methods and teams to make sure that it gets the attention it requires. Charles River, for example, has set up an internal data integrity governance committee made up of key business and regulatory executive leaders, to set goals and assess performance. The company articulates its approach and expectations for data integrity in a global quality policy and has two different plans in place for the business: a global data integrity
compliance plan for all its divisions and a CGLP-specific compliance plan. “Ex-
tensive CGLP training, with a focus on data integrity throughout, is included in
the training program for personnel engaged in pre-clinical work,” Catricks
says. All equipment and instruments that are used in CGLP studies are subject to
stringent validation and qualification re-
quirements, she says, based on standards
that ensure data integrity.

“The assurance of data integrity is not a
new expectation or concept, but over the
past few years there has been an increased
focus on data integrity within the indus-
try. I think there are times when staff at
laboratories that are conducting CGLP
work may not have a full understand-
ing of the CGLPs or the quality systems
that must be in place to ensure the CGLP
regulatory requirements have been met.
Unfortunately, this will result in studies
that cannot be reproduced and will lead to
instances in which FDA rejects studies
because the agency cannot confirm data
integrity,” Catricks says.

She suggests process mapping as
a useful tool for laboratory managers
who want to improve or enhance their
pre-clinical research programs. This
approach requires staff to take a critical
look at all the steps involved in a partic-
ular process to determine whether there
are any that are unnecessary or do not
add value, and then remove those steps. It
also calls for a close examination of areas
where there may be gaps in data integrity.

Laboratories interested in establishing
a CGLP program should engage with
partners that understand CGLPs, includ-
ing the preambles, and have expertise
working in an established CGLP envi-
ronment. “Simply reading the CGLPs is
not sufficient,” Catricks says.

New tools streamline efforts
Both sponsors and CROs are using and de-
veloping new tools to improve pre-clin-
tical testing efficiency. A number are
working with machine learning. One
such tool is the pre-clinical data integra-
tion and capture tool, PreDICT, de-
veloped by AstraZeneca and Tessella to ac-
cess, share, and analyze different types of
pre-clinical data. The software can pre-
dict optimal doses and scheduling. So far,
AstraZeneca reports using it for more than
150 projects, and notes that it has saved
30% of the time usually required
for pharmacokinetic/pharmacodynamic
models. In addition, the company claims
that use of the software has saved 1.5 to 2
days of study time for drug, metabolism,
and pharmacokinetics as well as biosci-
ence studies (3).

Also leveraging machine learning is
Riffyn, a company that started up six
years ago, which offers a cloud-based plat-
form, SDE, short for Scientific Develop-
ment Environment, for pre-clinical and
other development work. The software
incorporates principles from Six Sigma’s
define, measure, analyze, improve, and
control (DMAIC), quality by design, and
measurement systems analysis, says CEO
Tim Gardner. Riffyn’s initial experience
was in industrial biotechnology, where
SDE was used by the enzyme manufactu-
er Novozymes to increase capacity
by an order of magnitude and cut time
to market by a factor of two, Gardner
says. The company is now working with
a number of pharmaceutical and biophar-
maceutical companies on pre-clinical
and other development programs, in-
cluding bioassays, formulations develop-
ment, and bioprocess development.

As Gardner explains, SDE is really a
digitized Process Lifecycle Management
environment. “It’s built around map-
ing production and analytical process
designs and specifications and then
accelerating the improvement cycles of
those processes until they are ready for
transfer to manufacturing.” In bioassay
development for one pharmaceutical cli-
ent, Gardner explains, the tool allowed
users to cut 2400 hours per year out of
the lab time required for assays, halving
workload for a group of four.

Clearly, machine learning and ar-
tificial intelligence, which are already
playing a more dominant role in drug
discovery, promise to be used in more
pre-clinical work, and beyond, in the
future. Not only sponsors, but a growing
number of CROs and contract develop-
ment and manufacturing organizations
are actively exploring the technology’s
potential.

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Bottom line, ICH Q9 is scheduled to be revised, but the sections to be revised have yet to be identified. There is no timeline available for completion of the revision. Industry has provided feedback to representatives of the EWG on some of their thoughts on what needs to be clarified so that implementation of an effective QRM program can be achieved, and the industry can drive toward continuous improvement realizing what Janet Woodcock, director of FDA’s Center for Drug Evaluation and Research, described as, “A maximally efficient, agile, flexible, pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight” (5).

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Ask the Expert — Contin. from page 58

Bottom line, ICH Q9 is scheduled to be revised, but the sections to be revised have yet to be identified. To accomplish the vision of making appropriate and acceptable risk-based decisions, QRM needs to be iterative and not a once-and-done exercise within the quality management system. An effective QRM system should implement a risk review program to facilitate continuous improvement efforts.

At the PDA conference, attendees were given an opportunity to tell EWG representatives what they felt needed to be added or clarified in ICH Q9. They were asked to answer the following question: If you could recommend changes to ICH Q9, Quality Risk Management, what would you recommend? The information will be provided to the EWG representatives for consideration when they begin work enhancing the document and will be posted on the PDA Letter website. Some of the recommendations were as follows:

- Ensure that QRM is recognized by FDA as a required quality system. Currently, the European Medicines Agency (EMA) is more likely to inspect for QRM. There should be consensus regarding more alignment between Europe and the United States on QRM.
- Include a standardized CAPA.
- Remove the perception that QRM is not enforced and not part of the quality system.
- Include language that drives a holistic systems approach.
- Provide examples or a case study featuring a QRM tool.
- Expand clarity on the training and documentation needed for applying QRM.
- Clarify difference between risk evaluation and risk control.
- Define roles, particularly decision-maker roles.
- Provide more guidance on risk acceptance.
- Provide additional examples such as how to apply QRM to legacy products.
- Include examples of communication flow.
- Clarify levels of maturity for QRM in enterprise risk management.
- Offer strategies for demonstrating QRM compliance to regulators.
- Recommend how to prioritize compliance versus patient safety concerns.
ICH to Revise Quality Risk Management Guideline

ICH will be taking industry comments under consideration when it revises its Q9 guideline in order to clarify QRM requirements, says Susan J. Schniepp, executive vice-president of post-approval pharma and distinguished fellow, Regulatory Compliance Associates.

Q. I have heard that the International Council for Harmonization’s (ICH’s) Q9 Quality Risk Management (1) is being revised. Do you know what the industry can expect to see with the new version of the document?

A. You have heard correctly. At the December 2019 PDA Quality Week, attendees learned that ICH Q9 Expert Working Group (EWG) Members will start working on revising the document at the 2020 spring meeting in Vancouver, Canada. The guideline was first published in 2005 and, at the time of publication, it offered an overview of general quality risk management (QRM) principles including an example of a risk management lifecycle approach. In addition, the guideline provided a list of risk tools and quality system areas critical to establishing and maintaining an effective risk management program. As stated on the ICH website, “This Guideline provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality. These aspects include development, manufacturing, distribution, and the inspection and submission/review processes throughout the lifecycle of drug substances, drug (medicinal) products, biological and biotechnological products (including the use of raw materials, solvents, excipients, packaging and labeling materials in drug (medicinal) products, biological and biotechnological products)” (2).

Over the past 15 years, the industry has tried to implement QRM principles as a part of their quality management systems. The introduction to ICH Q9 states, “Although there are some examples of the use of QRM in the Pharma industry today, they are limited and do not represent the full contributions that risk management has to offer” (1). This statement still holds true today as citations for incomplete corrective action and preventative action (CAPA)/investigations typically ranks in the top five inspectional observations for the pharmaceutical and biopharmaceutical industries. To date, QRM implementation has used simple investigational tools to solve simple problems. In addition, the industry seems to struggle with providing data or metrics to demonstrate that information from investigation results have been used to effect continuous improvement. Speakers at the PDA conference also talked about some of the challenges the industry has faced in trying to implement QRM. These reasons include using QRM to justify actions instead of assessing risk and substituting risk-assessment tools for the QRM process (3). Other problems that seem to prevent effective implementation of QRM is using it to confirm a hypothesis or rationalize non-compliance situations (4).

Understanding the original purpose of ICH Q9 is crucial in understanding what the industry might see in terms of its revision.

Understanding the original purpose of ICH Q9 is crucial in understanding what the industry might see in terms of its revision. Current thinking, as discussed at the PDA conference, is that the EWG will focus on clarifying certain aspects of the document’s concepts in an addendum to the document. Basically, the document itself will probably not be revised but instead will be enhanced by creating a partnering document that will focus more on ‘how to do’ and less on ‘what to do’ with respect to QRM. The ICH Steering Committee approved the Q9 revised concept paper in November 2019, and the EWG is expected to begin working on the revision at the ICH spring meeting. A development integrated addendum according to ICH parlance means only specific sections of the guideline will be targeted for revision but a complete revision is off the table (4).

It is unclear whether the ICH Q9 revision will become more of a QRM tutorial or whether it will clarify what needs to be done (4).

Your opinion matters.
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