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COVER STORY

10 Biopharma Analysis Benefits from New Technology and Methods
Analytical solutions are improving for raw material testing, process development, drug product release, and more.

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The Call for a Rapid Response

An outbreak of viral pneumonia cases in Wuhan, China at the end of 2019 sparked fears 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 at medical and bio/pharmaceutical research organizations 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—reported small numbers of suspected or confirmed cases. Authorities in China implemented public health measures, enforcing aggressive travel restrictions and screening programs. Other countries screened travelers arriving from China or banned travel entirely.

Meanwhile, the medical research and pharmaceutical communities scrambled to answer basic questions about the virus using lessons learned from the SARS and MERS outbreaks. Following the previous outbreaks, the World Health Organization (WHO) placed the SARS-CoV and MERS-CoV on its Priority Pathogen list, encouraging research and the development of countermeasures against CoVs.

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 antivirals and vaccines for treatment (1). A genomic sequence of 2019-nCoV has been released to public databases, enabling researchers around the world to help find clues to detection of the virus and potential treatment options. 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 (2).

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 (3).

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

References
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Rising imports of drugs and APIs, at a time when FDA is struggling to inspect and oversee foreign manufacturers, have 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 that were contaminated by trace amounts of carcinogens.

Janet Woodcock, director of FDA’s Center for Drug Evaluation and Research, had the unenviable task of explaining how the agency was addressing these issues. She acknowledged in December that FDA was conducting fewer inspections of foreign drug producers, largely due to difficulties in hiring and training sufficient numbers of investigators to conduct site visits overseas. But she also reported a decline in never-inspected foreign sites and a rise in the number of facilities rated acceptable by the agency (1).

In response to concerns raised in a report from an 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. Regulatory authorities in all regions are working to improve the effectiveness and quality of GMP inspections.
and other nations through increased participation in Mutual Recognition Agreements (MRAs) with other capable inspectors. 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 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 production sites on “quality maturity,” a desirable status that a firm could promote to customers and investors. And high-quality continuous manufacturing systems, she predicted, would reduce waste from failed batches and thus lower costs significantly.

FDA looks to reduce the need to inspect certain manufacturing facilities in Europe and other nations through increased participation in MRAs.

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 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
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. New analytical techniques and methods are therefore crucial to the fast-moving bio/pharma industry.

“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.

MAJOR STRIDES IN ANALYTICAL METHODS
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–monoclonal antibody proteins (e.g., fusion proteins), bispecifics, and combination products in the product pipeline, however, is presenting
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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 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 ANALYTICAL 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.

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.

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, CGE, 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 addition,” he says, “late-stage programs with QbD filings are also exploring better turnaround times to support expanding pipelines.”

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 sig-
Harmonizing method development

Initiatives within the International Council for Harmonization (ICH) and the US Pharmacopeial Convention (USP) are focused on replacing the traditional development-validation-transfer approach to management of analytical procedures to one based on lifecycle management. “This approach,” asserts Geoff Carr, director of analytical development in Canada with Thermo Fisher Scientific, “requires rational development/validation coupled with a process of performance monitoring that leads to continuous improvements.”

These changes relate to an important development noted by Amit Katiyar, director of analytical and formulation development for bioprocess sciences at Thermo Fisher Scientific; the adoption of phase-appropriate analytical workflows combined with increasing harmonization of workflows across sites and with external partners, such as contract research and development organizations.

Phase-appropriate development and manufacturing can help pharma companies better handle their expanding product pipelines by enabling the supply of safe clinical materials while maintaining flexibility in manufacturing operations, according to Katiyar. He does note, however, that while ICH guidelines are defined for late-stage development, there is a lack of clarity on the qualification of analytical methods for early phase development.

“Harmonization using a platform approach to method development and qualification for early and late-stage projects and method validation for late-stage projects, as well as forced-degradation, research comparability, and formal comparability studies and specification setting has provided the opportunity to engage process development, analytical development, operations, quality, and regulatory organizations earlier in the development cycle,” Katiyar says. “The harmonized approach creates a well-defined roadmap for process development and operations teams to execute the program timelines in an efficient manner,” he adds.

The details of each harmonization approach vary from company to company. In some cases, the harmonized templates may contain specific experiments and acceptance criteria to ensure a successful platform approach, according to Katiyar. In other cases, high-level harmonization guidance provides flexibility during development.

“Pre-approved generic templates for draft methods, qualification plans, and forced degradation/comparability protocols result in higher productivity due to time savings resulting from a shorter review process for every program,” Katiyar observes. While there may be a need to modify the templates as reflected by the development data, he notes that such changes can be incorporated in the molecule-specific methods/plans, and protocols and subsequent changes can be reviewed by appropriate stakeholders for quality and regulatory compliance.

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.

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.”

Carr, meanwhile, expects to see increasing use 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/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, Katiya 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 OF ANALYTICAL TECHNOLOGY
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 pro-
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Cell Therapies: The Living End of Growth Opportunities

The commercialization of cell therapies is still at its infancy, but industry is facing an exciting period of development as the sector is expected to grow exponentially.

FELICITY THOMAS

As the incidence of chronic diseases, such as cancer, is rising, so too is the interest from industry in the area of cell and gene therapies. According to market research, the global cell and gene therapy market is projected to grow at a compound annual growth rate of 24% between 2018 and 2024 (1), driven by the increasing prevalence of chronic diseases, launch of new products, regulatory support, and improved manufacturing expertise.

“The entire cell therapy field is in its infancy,” confirms Jason Fontenot, senior vice-president, Cell Therapy, Sangamo Therapeutics. “Every aspect of cell therapy is in an exponential growth phase.”

KEY MARKET ASPECTS

Martin Lachs, head of the Oncology and Cell Therapeutics Project Management Group at ICON, an Ireland-based clinical research organization, notes that the promise of personalized medicines has been anticipated for a long time, with tangible and real effects of years of research into the human genome finally coming to fruition. “While oncology was the initial focus in cell and gene therapies, we’re now seeing a significant pipeline for rare/orphan diseases and other therapeutic areas,” he says. “At a recent conference on regenerative medicine (2), it was estimated there are over 1000 cell and gene therapy trials globally (650 in oncology)—and over 100 of them have received designations for expedited approval.”

A main driver of growth in cell and gene therapies for Keith Thompson, chief executive officer at the Cell and Gene Therapy Catapult (CGT Catapult), has been the impact of chimeric antigen receptor T cell (CAR-T cell) therapies. “These therapies use the genetic modification of cells to augment the cell-mediated immune response,” he adds. “Of particular note is the well documented successes of CAR-T cell therapies for hematological malignancies, which have transformed the therapeutic landscape and paved the way for a surge in cell and gene therapy trials.”

Industry has invested hugely in autologous CAR-T therapies following the approval of the first CD19 tar-
geted CAR-T therapies, specifies Fontenot. “The major areas of innovation within oncology cell therapy are ‘off-the-shelf’/allogeneic approaches and natural killer (NK) cell approaches,” he continues.

“Arguably,” says Lachs, “the commercially approved cell therapies Yescarta (axicabtagene ciloleucel) and Kymriah (tisagenlecleucel) have not realized the full potential hoped for in the marketplace as first-generation marketed CAR-T products. Even with such CD-19 targeted products, the trajectory is to bring these approaches closer to front-line treatment as opposed to limiting to relapsed refractory acute lymphocytic leukemia or lymphoma and to improve safety and durability of response.”

For Lachs, the next product that will be seen on the market will be autologous B cell maturation antigen (BCMA) target CAR-T cells in multiple myeloma. “Approaches to circumvent antigen escape, T-cell exhaustion, and so on, are focus areas with the advent of bi-specific constructs, for example,” he adds. “Additionally, combinatorial approaches with other immune regulating antibodies that impact the tumor/immune environment such as PD-1 are potentially promising.”

New indications have also been making waves in the industry. “Research into overcoming barriers to the use of genetically modified immune cell therapies for solid tumors is ongoing and showing promising results, especially with T-cell-receptor-engineered T cells showing great potential,” notes Thompson.

LIVING MEDICINES
The very nature of cell therapies, the fact that they are “living” drugs, makes their development much more complex than for other biological therapies, explains Fontenot. “The major challenge in cell therapy is developing a very defined drug product in which there are well-defined characteristics that are correlated with outcomes,” he says. “The donor-to-donor variation and the manufacturing process can introduce a huge amount of variability into the product and it is often unclear which attributes are driving efficacy and safety.”

Manufacturing and logistics are key differentiating factors between cell therapies and other biologics in Lachs’ opinion. “Producing viable, sterile autologous cell products that are also not contaminated with tumor cells and moving starting materials—the patient’s own cells—through the vein-to-vein process is certainly fraught and requires extraordinarily tight control,” he stresses. “The growth of specialist software platforms and logistics companies is a testimony to those challenges.”

Additionally, the growth of contract development and manufacturing organizations (CDMOs) to take on the burden of manufacturing cell therapies is a signal of the complexities of development of these therapies, Lachs continues. “For allogeneic products that use donor cells to treat many patients, the challenges of cell therapy development are somewhat ameliorated such as viability, but they are by no means dispensed with as the potential development of graft versus host disease comes into play,” he notes. “Maintaining chain of custody, chain of condition, and chain of identity are critical elements in a very complex supply chain that involves numerous stakeholders and handoffs.”

The uniqueness of cell therapies—the fact that they are living medicines and, when autologous, personalized to the patient—leads to significant therapeutic advantages, such as increased effectiveness and reduced chance of host rejection. However, Thompson emphasizes that the therapies also give rise to challenges throughout the manufacturing and product cycle.

“Each patient sample requires its own process,” he says. “A specialized manufacturing process is vital to ensure that these living medicines are developed safely, efficiently, and do not compromise the sample. Autologous cell therapies don’t require a scale-up of production (larger volume), but rather a scale-out (i.e., a larger number of parallel processes) to be able to manufacture at scale. Because of this, many of the manufacturing processes, facilities, and regulations required to produce cell therapies have only been established in the last few years as therapies started to reach clinics.”

Handling of cell therapies is also unique, with timing critical and tracking equally so, due to safety and the irreplaceable nature of the starting materials, Thompson asserts. “Particularly for autologous therapies, quality is an important consideration,” he says. “Further challenges in development may arise because the initial sample can be compromised as a result of the patient’s disease.”

Furthermore, regulations are inevitably more complex. “Cell therapies often involve multiple elements, such as gene modification, activation of cells using viruses or other vectors, which need to be tightly regulated,” Thompson adds.

DEVELOPMENT CHALLENGES
An overwhelming challenge for developers of cell therapies is cost. These complex therapies are expensive to progress through the various development cycles and, given the manufacturing and logistics challenges that they give rise to, funding is more than likely required via venture capital or collaborations. “The stop-start nature of trials owing to rapidly emerging (safety) data, which results in numer-
ous protocol amendments, manufacturing glitches etc., places profound pressure on the development cycle,” confirms Lachs.

The lack of long-term data could be adding to the development challenges of cell therapies. “Despite the fact that the results being seen from currently available therapies are remarkable, evidence for long-term efficacy is still accumulating,” says Thompson. “Added to the production costs required for cell therapies, additional questions are raised over the suitability of current reimbursement schemes.”

Access to autologous cell therapies is also challenging. “Off-the-shelf approaches are the future,” states Fontenot. “Developing drug product attributes (i.e., cell phenotype of functional measurements) that are well correlated with outcomes is important but very difficult. Also, animal models are even more limiting than in the small molecule and biologics spaces. One can only use immunodeficient animal models to evaluate human cell therapies, which is very limiting.”

As companies start to move towards solid tumor targets, the ability to obtain tissue for the production or expansion of cell therapies adds another burden, continues Lachs. “The treatment of patients with advanced solid tumors has become more dependent on tissue biomarkers to help guide management decisions,” he says. “Targeted therapies are associated with superior clinical outcomes, but to obtain updated biomarkers and targets, large biopsy specimens are often needed. This not always feasible either because the lesion(s) are not safely accessible to a surgeon or an interventional radiologist, or because the patient declines further invasive procedures.”

From a commercialization perspective, the cleanroom space to enable manufacture of cell therapies at scale could be problematic, notes Thompson. “Additionally, as companies progress towards commercialization of cell therapies, they require more personnel with the specialist skills required, but the appropriate schemes need to be put in place to provide training in these skills and widen the talent pool,” he says.

**AVAILABLE SOLUTIONS**

There are several potential solutions available that could help overcome some of the challenges associated with cell and gene therapy development. “Renewable cell-source-derived (e.g., induced pluripotent stem cell [iPSC]-derived) cell therapies have the potential to greatly increase patient access and introduce more uniformity into the process,” states Fontenot. “Using ‘omics’ approaches to characterize the drug product pre-infusion and for follow up of patients post treatment is also a major area of focus, as it can help identify key attributes to correlate phenotypes and outcomes.”

Specifically looking at the United Kingdom, Thompson reveals that a collaborative ecosystem, where companies can work with government agencies, regulatory bodies, the industry, and healthcare system, can prove to be advantageous. Moreover, strong government support of facilities, such as the Cell and Gene Therapy Catapult development and manufacturing centers, and initiatives that have been set up to help companies, such as the Advanced Therapies Apprenticeship Community, can aid development of advanced therapies and growth of the industry, he adds.

In addition to the many approaches available to tackle the scientific challenges, costs associated with cell therapy development may, in part, be addressed via successful allogeneic or ‘off-the-shelf’ products. “Allogeneic or ‘off-the-shelf’ products avoid some of the obvious logistical complexities of modifying the patient’s own cells and all that this entails,” Lachs says. “Obtaining cells from healthy individuals improves the likely viability of cells circumventing T-cell exhaustion and contamination with rogue cells. That is not a sure thing.”

However, Lachs warns that allogeneic approaches need to circumnavigate the tissue-matching phenomenon, which means that human leukocyte antigen typing becomes key in many, but not all, cases, potentially limiting the target population. “Generally, it is held that graft versus host disease is not a major feature for allogeneic T-cells in more advanced development,” he says. “The ability to produce hundreds of viable cells for multiple infusion is very compelling from a treatment and cost perspective.”

“There is a long-standing desire to move from autologous to allogeneic CAR-T cell therapies, predominantly because of the improvements ‘off-the-shelf’ therapies promise for the accessibility, logistics, and cost of CAR-T cell therapies,” Thompson confirms. “Other potential benefits of allogeneic CAR-T cell therapies are that samples would be provided by healthy donors, and they could be used more immediately than autologous therapies thus limiting disease progression during the manufacturing process.”

**FUTURE TRENDS**

In Lachs’ opinion, there will be three areas that will witness significant developments over the next 10 years. Firstly, he expects that industry will conquer the obstacles created by the local tumor environment, opening the opportunity to successfully tackle a broader range of particularly solid tumors. Secondly, he notes that “manufacturing of cell therapies will become automated and much cheaper, making the generation of both allogeneic and autologous cell products faster, easier, and cheaper.” He adds that, “both allogeneic and autologous approaches will have a role in the future, and one will not supplant the other.” Thirdly, Lachs continues, “cell therapies will
find extended utility in a breadth of therapeutic indications, such as neurodegenerative disorders and rarer enzymatic pathologies.”

Agreeing with Lachs, in part, Fontenot specifies that major trends will be the use of cell therapies outside of oncology, in addition to “off-the-shelf” options. “Renewable cell-source-derived products will be a huge focus,” he says. “The other trend will be toward more highly engineered products—more gene editing, more complex engineering. I believe the next major breakthrough will be engineered regulatory T cells. I am convinced that these cell products have the potential to cure autoimmune diseases.”

Further commenting on gene editing, Thompson adds that it will have a crucial role over the next decade as researchers search for new ways to target and treat the underlying causes of diseases, as well as accelerate advanced therapy development. “Pluripotent stem cells have long held the promise of producing major classes of stem cell-derived treatments; however, this field has somewhat lagged the gene therapy and gene-modified cell therapy field,” he notes. “Much of the enabling work has taken place with embryonic stem cells, and we have seen some results in the clinic, for example in ophthalmology and diabetes. Significant investment has gone into iPSC-derived cell therapies, and we are now seeing expanded corporate activity. We expect to see more early stage clinical work which, if successful, is likely to drive another big wave of investment and clinical development.”

Methods used to scale up vector production for clinical trials and commercial supply will also be an area that will see progression, according to Thompson. “Advancements in methods used to scale up vector production will be essential to meet demand as the number of trials and approved therapies continues to grow,” he says. “And as already discussed, there will certainly be developments and new generations of cell therapies of all types and modalities for a wider range of diseases, and new strategies will emerge to improve the manufacture and delivery of autologous and allogeneic therapies. It’s truly an exciting time for developers in the industry as we start the new decade.”

“While we are continually challenged with lack of standardized processes and systems, the industry will continue to learn and evolve with best practices to support scalability and access,” concludes Lachs. “It’s indeed an exciting time in medicine understanding that cell and gene therapies work—and save lives.”

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Cell Culture Variables for Gene Therapy Vectors

The production of viral vectors for use in gene therapy benefits from being able to use similar cell-culture processes as mAbs, but it faces limitations under current cell-culture technologies.

Much attention is focused on the use of viral vectors as the delivery vehicle for gene therapy because of their ability to target specific cells, attach to the cell, and inject genetic material into the cell, which is a critical mechanism for a gene therapy. The structure of a viral vector, empty of its own DNA, makes for practical “housing” for the DNA, RNA, or other genetic material that is the therapy. Other forms of packaging for genetic material may work as a “housing” structure but lack the mechanism to deliver the therapy once in vivo. Several virus types have been investigated for use as gene therapy delivery vectors, including retroviruses, adenoviruses, adeno-associated viruses (AAV), poxviruses, rhabdoviruses, parvoviruses, and alpha viruses (1).

SIMILARITIES TO mAbs
Viral vectors are cultivated in a similar manner to monoclonal antibodies (mAbs) in that the vectors can be mass produced in cell culture. This offers the advantages of having technology, processes, equipment, know-how, and infrastructure that are already established and that have been standardized. “Both can share many similarities when based upon suspension cell cultures (Chinese hamster ovary [CHO] and adapted human embryonic kidney–293 [HEK–293] cells) where similar concerns are in play: cell growth, pH control, dissolved oxygen control, sufficient mixing, shear avoidance, etc.,” says Tony W. Hsiao, staff engineer, R&D, at Thermo Fisher Scientific. “They may differ, however, in that some viral vector processes have a need for adherent or even non-mammalian (Spodoptera frugiperda 9 [SF9]) cell cultures that are less common in standard mAb production.”

“There are a number of similarities ranging from culture vessels (i.e., shake flasks, WAVE bioreactor, stirred tank reactors, etc.) and media formulations, but there are several important distinctions,” say experts at Novartis. “For example, the most commonly used mammalian cell lines for viral vector manufacturing are HEK-293 derived, whereas the overwhelming majority of antibody and recombinant protein production processes utilize stable CHO-derived cell lines.”
Furthermore, antibody and recombinant protein production processes are increasingly implementing continuous processing (i.e., perfusion) while many viral vector manufacturing processes still utilize fed-batch processes, focusing instead on the transfection step, the Novartis experts note.

Cell culture for AAV viral vectors is particularly similar to mAb cell culture, including the fact that the basis of the cell-culture process for both are mammalian cells, adds Diane Blumenthal, head, technical operations, Spark Therapeutics. “We use reactors that are the same, albeit much smaller, as the amount of product needed for the patient population is smaller. We are often tackling diseases that are rare. As we put gene therapy to use where patient populations are larger, the scale will be larger.”

To emphasize the difference in output of therapeutic antibodies versus viral vectors for gene therapy, Blumenthal points out that antibodies are produced in bioreactors of 10,000 L in size or larger (commercial stainless-steel bioreactors), whereas AAV viral vectors are produced in volumes of 200 L to 500 L. “There may be some [AAV viral vector production] even larger at 2000 L, but I am not aware of any being utilized for larger stage product development,” Blumenthal says.

“What is different is that we are using mammalian cells to make a virus as opposed to a protein,” she continues. In antibody production, the mammalian cells are modified to express the antibody of interest, but in viral vector production, the mammalian cells are treated to make them porous. This then allows the cells to take up plasmid DNA, which encodes for the production of virus. “The mammalian cell becomes the factory for the production of virus containing the gene of interest to be delivered to patient cells,” Blumenthal explains.

The similarities to mAb cell culture benefit viral vectors. “In many ways, techniques that are now well established for antibody production can be applied to viral vector manufacturing. These include: metabolic flux analysis, bioreactor optimization based on mass transfer scale-up, and media and feed development. In addition, best practices around cell bank safety testing and genetic stability for cell lines (established with antibody producing cell lines) can be leveraged for viral vector manufacturing,” the Novartis experts state.

“It would seem that viral-vector manufacturing has the fortune of being able to leap-frog some technology development steps and jump right in line with where existing biopharma currently is,” Hsiao contemplates. “There is a bevy of tools and technologies available that have been put through their paces and available for deployment in current good manufacturing practices (cGMP) processes for making approved commercial products. The essential steps of scaling up cells, traversing seed trains, and reaching production volume are well established,” he notes.

“The nuances of proper transfection, optimization, reproducibility, and maximizing ergonomics are all areas that will require some development and for viral producers to potentially blaze new trails,” Hsiao adds.

**WHERE THEY DIFFER**

The differences in the cell culture process between mAbs and viral vectors may also vary (e.g., media, buffers, equipment, processing techniques, etc.). For instance, media formulations themselves may differ as there may be different goals in production (e.g., cell health, protein production, or transfection susceptibility), but an emphasis on details, such as defined compositions, animal-origin free (AOF) components, or others, are always in play, notes Hsiao. “Current viral processes are largely batch processes of shorter duration, so media nutrient loading may also differ,” Hsiao says.

“As for the equipment, similar stirred tank reactor (STR) systems are a straightforward option for suspension processes (mammalian or other). For adherent cell systems, alternatives include microcarriers in STRs, packed bed reactors, or roller bottles/multi-layer planar systems. The decision of which system to use is largely driven by capabilities and volume demands,” he adds.

Meanwhile, regarding techniques, overall aseptic concerns are similar, but a higher biosafety level for the facility is needed to support human cell lines and potentially infective viruses and particles, Hsiao points out. “Similarly, standard 0.2-micron filters used in many antibody processes may or may not be sufficient in applications involving viruses, particularly when considering cross-contamination and operator safety,” he says.

For AAV manufacture, Blumenthal emphasizes the media, buffers, and equipment are similar. “The main difference is in the solutions needed for the transfection step. In addition, the sterile technique is similar when cultivating cells in bioreactors unless you are using roller bottles, which are more of a manual process and require manipulations to be done under laminar flow,” she says.

The Novartis experts weigh in as well, saying that there are differences between mAb and viral vector cell culture, but that those differences can be thought of as pertaining to the different cell lines (HEK-293 for viral vectors, CHO for antibodies) with different growth characteristics and different metabolic profiles. “Generally speaking, CHO cells tend to be more robust when it comes to tolerating stresses (shear forces, pH, or temperature excursions, etc.), but viral vector manufacturing is typically carried out at a smaller scale than antibody production due to inefficiencies in transfection at large scale and instability in viral particles upon passaging. In addition, common bioprocessing steps, such as filtration, are more challenging with viral vector manufacturing because

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Challenges in Vector Purification for Gene Therapy

Developers need to transcend the limits of existing separation technologies, to maximize vector recovery while preserving therapeutic potency.

FELIZA MIRASOL

The downstream processing of viral vectors used in gene therapy poses tough challenges, including the limitations of existing separation and purification technologies. Even though there are many different ways to purify viral vectors, these processes all suffer from drawbacks: either they lack the scalability required to purify large quantities of vector or they require numerous inefficient steps, making them cost prohibitive. Scalable purification technologies are needed that are robust, cost-effective, and applicable to different gene therapy products (i.e., to both viral and non-viral vectors) (1–3).

Viral vectors, size is a limiting factor in downstream processing. Viral molecules are far larger and heavier than other therapeutic proteins that undergo separation and purification. Where the size range for proteins typically runs from 0.005 to 0.08 × 10^6 Da, viruses often exceed 5 × 10^6 Da, and some can be as large as 1000 nm (3). As a result, developers cannot simply put viral molecules through the same processing steps using the equipment used for antibodies or other therapeutic proteins and expect similar results.

Over the years, size-based viral purification strategies have included density-gradient ultracentrifugation, ultrafiltration, precipitation, two-phase extraction systems, and size-exclusion chromatography (SEC). Affinity chromatography is often favored as a more viable process because of its robustness and high selectivity. However, it requires the use of resin, and currently, there exist only a small number of single-serotype targeted affinity resins (i.e., resin that can be used for only one virus serotype). In order for the process to be economically viable, the resin must be reusable multiple times and be applicable to multiple serotypes (1,4).

VIRUS TYPES

Four main types of virus, each with multiple serotypes, have been studied for use as vectors in gene therapy: adenovirus, lentivirus, retrovirus, and adeno-associated virus (AAV). The most widely used is AAV, which has shown great potential as a gene-delivery vehicle in clinical studies (1, 4).
AAVs can primarily be released by cells in the upstream cell-culture process without the need for lysis, which simplifies harvesting and purification steps by minimizing the amount of cell debris. However, without cell lysis, some AAVs may remain inside the host cell, and require intentional disruption of the cell membrane to release product. What’s more, AAV particles can be sticky and adhere to cell debris in the culture media, which can cause low yields downstream.

**BIOLOGICAL CHALLENGES**

One of the greatest challenges in viral vector production occurs during transfection, when the genetic material for the therapy is introduced to the viral vector. This has to do with the viral capsids within which the genetic material is encapsulated. Vectors that do not take up the genetic material will remain empty and be processed along with the full vectors downstream, which can result in final dosage forms that contain a mix of empty and full vectors.

Whether they are full or empty, viral capsids exhibit similar measurable biophysical properties, making it difficult to distinguish between them, and separate them. So far, the industry has not standardized on an optimal full-to-empty ratio for capsids, leaving uncertainty as to how variability in that ratio affects patient dosing. A large number of empty vectors, for example, may result in patients needing a higher dose of the therapy, which can place unnecessary stress on the immune system, and potentially lead to adverse immune responses.

At present, only a few commercially available resins are offered that can separate full from empty viral capsids during chromatography (2). As research continues into understanding the nuances of viral biology, the industry can expect to see improvements in the types of downstream processing technologies that can be used to purify viral vectors for gene therapy. Smarter strategies may incorporate combinations of traditional approaches with new technologies leading to the development of robust and economical platforms.

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Fresh Thinking in Biologic Drug Formulation

Biologics raise unique formulation and development challenges, and industry is still on a learning curve to get the best out of these diverse and complex therapies.

FELICITY THOMAS

The global biologics market has experienced significant growth over recent years and, according to market research, is expected to continue to grow in the near future, potentially being worth $625.6 million by 2026 (1). Advancement of the sector is projected to be driven by an increase in prevalence of chronic conditions, technological advancements, mergers and acquisitions, more market approvals, and the development of more efficient biologics (1).

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

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

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

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

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

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

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

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

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

To overcome the enzymatic and pH-dependent degradation of drugs in the stomach, in addition to permeability issues and the potential for degradation via first pass metabolism, formulation strategies, such as enzymatic activity inhibitors, permeation enhancers, enteric coatings, and carrier molecules, can be employed, Costa reveals.

“The increased focus on inhalation delivery reflects the benefits offered by this route of administration,” Costa continues. “Delivery by inhalation bypasses the harsh conditions in the gastrointestinal tract, allowing the administration of lower doses with reduced side effects, particularly for respiratory drugs delivered directly to the site of action.”

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

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

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

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

REFORMULATION AND SELF-ADMINISTRATION
SC administration of biologics, in particular antibodies, is a strategy being employed by industry to improve patient comfort and provide

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Bioprocess for Beginners:  
From Shaker to Bioreactor

An interview with David Solbach,  
M.Sc., Scientific Communications  
Manager at Eppendorf AG Bio Process Center.

A new eight-blade impeller is designed to ensure  
gentle mixing and reduced cell settling compared to  
pitched-blade impellers at the same agitation speed.

S tem cell-based technologies are one of the most promising approaches in the  
advancement of cell therapy and regenerative medicine. To make progress towards  
commercialization, researchers are evaluating standardization of their cultivation and  
efficient scale-up.

David Solbach, M.Sc., Scientific Communications Manager at Eppendorf AG BioProcess  
Center, recently spoke with BioPharm International about the advantages of changing  
from shake flasks to stirred-tank bioreactors, the problems that can occur, and aspects  
to consider to ensure proper cell growth.

BioPharm: Why switch from a shaker  
to a bioreactor?

Solbach: This is a commonly asked  
question, especially from scientists who  
work with flasks and plates and are afraid of  
switching to a stirred-tank bioreactor. Shake  
flasks are an easy-to-use and inexpensive  
choice for basic applications and do not  
need advanced equipment or sensing and  
control technologies. However, this very  
simplicity is also the biggest disadvantage.  
For example, there is already a significant  
difference between shaking and stirring in  
terms of fluid dynamics, which are directly  
influenced by the agitation mode, stirring  
direction and speed. This has a direct  
impact on parameters like heat transfer and  
cell homogeneity. A bioreactor provides  
diverse insights into culture performance  
and the opportunity to monitor and control  
the process parameters at any given time  
point. Thus, critical parameters can be  
adjusted, including temperature, dissolved  
oxygen, or pH on demand, or an automated  
process can be programmed.

BioPharm: Where do you see the  
biggest potential in using bioreactors?

Solbach: The biggest advantage can be  
found in the possibility of automation,  
constant monitoring of a process, and  
automated adaptions controlled by  
intelligent software to decrease the risk of  
failures that naturally appear when multiple  
manual steps are involved. Consider the  
risk of a contamination, especially when  
working in larger volumes such as hundreds  
of liters. Stem cell media is quite expensive  
and can be lost to contamination.

For stem cell customers, another  
advantage is the availability of single-use  
vessels. For example, our BioBLU Single-  
Use Vessels are pre-sterilized and strongly  
reduce the risk of cross-contamination,  
which might appear with traditional glass  
vessels as a result of failures during the  
sterilization process. An additional  
advantage of single-use vessels is they  
are lighter weight than glass vessels,  
which makes them easier to handle.
**BioPharm:** What aspects need to be considered when scaling up with a bioreactor?

**Solbach:** There are several things to consider. One of the most important parameters is oxygen. The availability of oxygen in a bioreactor is the key to success for bioprocessing. For a microbial fermentation, it is fairly easy to ensure proper oxygen supply because bacteria cells are more robust than stem cells. A Rushton-type impeller with high agitation speed can ensure good oxygen transfer to the medium. In contrast, stem cells are very sensitive to shear stress and have to be treated carefully. Therefore, an impeller with pitched blades and slow agitation speeds is typically used to ensure gentle culture mixing.

The availability of oxygen in a bioreactor is the key to success for bioprocessing.

In bioprocessing, the oxygen transfer rate (OTR) describes the oxygen transfer from a gauge space to the culture medium. The OTR is considered a key engineering process parameter to culture scale-up and is influenced by many different factors: bioreactor dimension, agitation speed, gas flow rate and concentration, and impeller design. Most scale-up strategies aim for keeping one or more parameters constant across scales. For example, it is important to adjust the stirring speed to maintain assimilative speed. For proper cell culture scale-up, it is important to select equipment of different sizes with similar kLa capabilities that offer sufficient overlapping so that the small-scale success can be replicated in larger volumes.

Stirred-tank bioreactors provide the design that is comparably easy to describe with classical engineering approaches such as the vessel geometry, impeller diameter, vessel diameter, liquid height and ratios. This is the design that most research concerning scale-up phenomena has been conducted on and was transferred to our single-use vessels.

**BioPharm:** Are there innovative impeller adaptions in the field of stem cell cultures?

**Solbach:** There is an increasing tendency in the field to move from shake flasks to stirred-tank bioreactors, especially with the focus on scaling up standardization and reproducibility. In classical microbiology, the Rushton-type impeller with high agitation speed is used, while for stem cell applications, a pitched-blade impeller with slow agitation is preferred to ensure equal mixing and low shear stress for the cells. This is one aspect that frightens stem cell scientists who start working with a bioreactor. Particularly with stem cell culture, it is important to find the right agitation speed that does not harm the cell while ensuring a good oxygen supply and prevents the cell from settling.

A pitched-blade impeller does a great job of mixing efficiency and low shear stress simultaneously. However, a common problem is that cells settle when the stirring speed is too slow. To overcome this challenge, Eppendorf has developed a new impeller with eight blades— together with Professor Zweigerdt from the Hannover Medical School—designed to keep cells in solution even at low stirring speeds. The eight-pitched blades ensure gentle mixing and reduce cell settling compared to pitched-blade impellers at the same agitation speed.

**BioPharm:** Can you provide an example of how automation in bioprocessing can be advantageous?

**Solbach:** Automation is especially useful for processes running in perfusion mode. In the Zweigerdt group, the effect of manual-fed-batch feeding and perfusion on the performance on cell growth have been tested. In the perfusion set-up, feeding and harvesting were automatically controlled, while in the fed-batch run, the medium was manually exchanged. The automated process not only decreased the workload, it also reduced the risk of contamination, which is highly undesirable when working with stem cell cultures. Cells grown in the perfusion set-up had an overall better performance resulting in a higher yield compared to the manual fed-batch run.

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**Eppendorf** is a leading life science company that develops and sells instruments, consumables, and services for liquid-, sample-, and cell-handling in laboratories worldwide.
The Need for Advanced Process Modeling for New Therapeutic Biologics

The trend toward personalized medicines includes more complex manufacturing cycles that can benefit from advanced process modeling early on in the therapeutics’ development.

FELIZA MIRASOL

Process modeling plays a crucial role in process development and in scaling up bioprocesses. As bioprocessing workflows increasingly shift toward automation, the approach to modeling also needs to evolve to incorporate next-generation tools and software. For example, how would process modeling take advantage of digitalization and artificial intelligence? The focus on precision medicines also means there is a need to develop a better or new understanding of workflows, whose efficiency and cost can be predicted through process modeling.

HOW MODELING FITS QbD

Nearly all aspects of biopharmaceutical processing technology use model-based methods because modeling can decrease the amount of experimental effort it would take to design a process while increasing the robustness of that process. Modeling can also provide process transparency, which in turn can clarify and highlight the rationale behind making certain decisions for the process. What’s more, process modeling can be implemented, and is strongly encouraged, early on in the lifecycle process of product development, as early as the preclinical stages. The modeling approach can also bring early consideration to the regulatory aspects of drug development and future commercialization, allowing process developers to troubleshoot what may be regulatory challenges or hurdles as they advance a product candidate. FDA’s quality-by-design (QbD) and validation initiatives also encourage the use of modeling early on.

While QbD does not define manufacturing design space or specific protocols, it does discuss the need for a systematic approach to drug development and manufacturing. FDA believes that a QbD approach, similar to process modeling, should start with predefined objectives. There should also be an emphasis on product understanding and process control, and
Artificial intelligence (AI) is starting to be used more and more as a tool that can help biopharmaceutical manufacturers do advanced modeling for production processes. One example of this is the Sartorius-Al-Lab (SAIL) established as a joint venture between Sartorius and the German Research Center for Artificial Intelligence (DFKI). The lab, launched in December 2019, is located on the DFKI campus in Kaiserslautern, Germany (1).

Sartorius and DFKI intend to use the lab for training purposes. The partners plan to develop and apply machine learning as well as image and pattern recognition processes that can be applied to life-sciences activities. Researchers, for instance, are working on new deep learning algorithms and methods for image recognition of cells and organoids, which can be applied to the analysis and modeling of biological systems. These advancements can also be used to simulate and, therefore, optimize biopharmaceutical production processes.

The partners have noted that the establishment of SAIL and their partnership will create foundations for the development of digital tools and AI-based methods in biopharmaceutical operations. The ultimate aim of using these next-generation tools is to develop better data analyses methods because modern methods are used only to a limited extent in the biopharma industry. In addition, development of AI-based methods and digital tools would conceivably provide greater computer capacities to map and simulate the development and manufacture of biopharmaceuticals through computer modeling, resulting in shorter development times and possibly lower development costs for new therapies—from idea through to patient.

Reference

that the design of a process should be grounded in “sound science” and quality risk management (1).

FDA has noted in the past that many innovator pharma companies have, for the most part, embraced the science and risk-based approaches in QbD and that other companies, such as generic and biotech companies, have started to adopt QbD as well (1). However, this is not necessarily the case for process modeling.

Despite the advantages that a model-based approach can confer, modeling is still not fully implemented by industry. For one thing, the model-based approach may not yet be fully accepted. Further, the industry lacks “user-friendly tools” and clear workflows for setting up specific process models, and existing process control systems do not implement model-based approaches (2).

While a model for a bioprocess can align bioprocess specifications with the technical framework needed to develop the required information technology (IT) around it, implementing a model for a bioprocess can be particularly challenging. For example, the bioprocess model would have to capture relevant information consistently as well as thoroughly to allow both researchers and IT developers understand the process requirements. The model would need to capture alternatives and exceptions to the standard, in addition to capturing normal operations, and, incorporating automation into the model, it must be easily executable.

TYPES OF MODELING APPROACHES
There are many different types of models used in the development of a new process for a novel therapeutic, says Andrew Sinclair, managing director, Biopharm Services, a UK-based developer of technology solutions and services for biopharmaceutical manufacturing. Sinclair notes that there are specific challenges to some of the newer personalized therapies and gives the following examples of modeling techniques that can be broken into several areas:

- Design of experiments and statistical analysis
- Deterministic models for optimization
- Scale-up models linked to experimental data
- Data modeling, analysis, and visualization
- Whole process modeling and optimization
- Economic analysis focusing on cost of ownership, cost of goods, and risk mitigation
- Supply chain modeling.

“Each has a role to play, the extent of which depends on the application,” Sinclair states. “Models are tools as a part of a toolset and are applied based on use case, so each modeling approach has different strengths and limitations depending on the actual application and product process approach.”

Advanced process modeling enables and supports the digitalization and automation of bioprocessing through the capture of large datasets, data analytics, and visualization, Sinclair adds. “Using model outputs linked with experimental and, where it exists, production data opens sig-
nificant opportunities to apply machine learning techniques and build knowledge that has applications across products.”

The ability for advanced process modeling to capture and analyze large datasets helps biomanufacturers make sense of all the data. “The use of structured data in large datasets opens significant opportunities both in terms of guiding future process development activities and improving the current set of predictive models. This is key to automating development activities and optimizing processes through machine learning, which will augment process modeling approaches,” says Sinclair.

PERSONALIZED MEDICINES
Having a model-based approach is especially useful for personalized medicines, which typically target niche disease markets and small patient populations, but for which each single dose is costly. Focusing on these new therapeutic areas brings up some key issues. For instance, Sinclair points out there is little fundamental understanding of these processes that can support deterministic modeling linked to process optimization. “Here, the emphasis is on statistical approaches,” he says.

An important requirement for the newer therapies is the need for supply-chain modeling, where there is a strict time limit from the point of taking cells from the patient to the return of the treatment to the patient, Sinclair emphasizes. In these cases, he continues, the process involves transportation and multiple centers for processing the material.

EARLIER IS BETTER
Process modeling has a significant role to play in the lifecycle of a therapeutic product. Because of this, generally, the earlier it is implemented, the better, as there is greater scope for optimization of the process, Sinclair says.

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

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

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Additional coverage can be found online.
Complex protein structures pose analytical challenges that can be addressed by advanced mass spectrometry technologies and workflows, which can be used to comprehensively characterize them.

AARON O. BAILEY

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

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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.

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 provides 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 Trivid 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 Trivid 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 digestion 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 MSn 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 MSn 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 the deconvolution of intact proteins “slides” along a chromatogram and acts 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 moves 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 bio-therapeutic 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.

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More on protein characterization

For more on protein characterization, read these articles on BioPharmInternational.com:
- Antibody Purification Process
- Development and Manufacturing
- Improving Oligonucleotide Analysis
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More on cell culture

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- The Evolving Role of Starting Materials in Cell and Gene Therapy
- Turning to Plant Cell Culture for Sustainability
Data Management Practices

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

LAUREN LAVELLE

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 sharing of data. To ensure proper data integrity procedures, the software, systems, and services should match the intended process.

LIMS AND ENL
Laboratory information management systems (LIMS) are software systems intended for the management of lab samples and data to improve record keeping and reporting, and to automate and streamline workflows (3). Because of their organized nature, LIMS are equipped 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.

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 (12).

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.

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Managing Risk for Cell and Gene Therapy Logistics

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

AGNES SHANLEY

The past few years have seen dramatic growth in cell and gene therapy research and commercialization. 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 biopharmaceutical and small molecules will not work in the evolving supply chain for autologous and allogeneic therapies. Manufacturing and transport involve many more diverse stakeholders and patient groups than traditional programs. For autologous therapies, there is a need to closely coordinate raw material extraction and therapy production, and the 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 alliance, the CDMO Lonza, the information technology (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 manufacturing execution system (MES) and electronic batch record (EBR) solution with Vineti’s supply chain orchestration platform, designed to connect manufacturers and healthcare providers at the point of care, in real time.

BUILT-FOR-PURPOSE IT SYSTEMS

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 his-
tory 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. 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 enable capacity optimization. “This approach will reduce the burden on biopharma manufacturing companies (i.e., CDMO customers), which will no longer have to handle CDMO data integration themselves, since the system will already be built for them to link into,” she says.

Cryoport’s Chief Commercial Officer Mark Sawicki discussed the work now underway in cell and gene therapies with Lonza and Vineti with BioPharm International.

COMPLEXITY AND CHALLENGES

BioPharm: 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.

In addition, the manufacturing processes associated with autologous therapies are not mature. As a result, you’re often extending 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 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.

BioPharm: What do these challenges mean for data management?

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.

INTEREST IN AI IS GROWING

BioPharm: What is required for interconnectivity, 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.

BioPharm: How do you connect to CDMOs and to the clinical side?

Sawicki: We typically connect through electronic data interchange or application programming interfaces 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 Vinetti’s platform. In some cases, elements of our IT system are 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

BioPharm: What led Cryoport to develop the special containers?

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'd see in a GMP manufacturing environment for the equipment used to transport these materials to end users. Some 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. 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.

BioPharm: What are you expecting in terms of standards (e.g., for good distribution practices for the new therapies)?

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 unusable. With many cell and gene therapies, deviations from prescribed environmental conditions, even those that last for a few milliseconds, can destroy product. There is no visible way to tell whether the cells are still usable 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 connect 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 period, they would be able to examine data and see any patterns that come up. We maintain all data generated by our systems and can go back nine years and provide regulators with any information they request.

BioPharm: Is there currently a bottleneck in the services available?

Sawicki: As more advanced therapy 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.

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.

BioPharm: How about scalability?

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 carry out the visual inspection that is required when releasing allogeneic product from a liquid nitrogen tank when performing visual inspection can potentially render product unusable? The industry must resolve many of these questions.◆

Scheduling pickups and deliveries can be very challenging, especially for autologous therapies.
when the new technology has the potential to improve product quality. The dilemma here, according to Carr, is that a new technique is sufficiently better than the currently accepted technique 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.

THE NEED TO 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 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 through the lifecycle of the program.

For Heewon Lee, director of analytical research and quality systems in chemical development US for Boehringer Ingelheim Pharmaceuticals, 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.

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.

Early engagement with health authorities is crucial for regulatory acceptance of novel technologies.

The need to collaborate
ICH Q9 is scheduled to be revised, but the sections to be revised have yet to be identified.

It is unclear whether the ICH Q9 revision will become more of a QRM tutorial or whether it will clarify what needs to be achieved in order for a QRM system to be considered robust and effective. 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.

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).

REFERENCES
1. ICH, Q9 Quality Risk Management, Step 4 version (2005).
2. ICH, Quality Guidelines, ICH.org.
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 preventive 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. 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).

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