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From the Editor

Rita Peters is the editorial director of BioPharm International.

Half a century after man first walked on the moon, space-based science is exploring benefits for Planet Earth.

The Moon, the Stars, and the Science Lab

The summer of 1969 was a watershed moment for science when, on July 20, man first walked on the Moon. The story of the Apollo 11 flight is well-known. Astronaut Neil Armstrong’s words as he stepped on to the surface, “That’s one small step for [a] man, one giant leap for mankind,” resounded around the world and became one of the most recognized quotes of a generation.

The technology used for the trip to the Moon pales in comparison to current materials, instruments, computing, and communication capabilities. The computing power in the Apollo 11 ship was less than that of an average cell phone today. The astronauts appeared ghostlike as they moved about the Moon; technology limits prevented transmission of higher resolution images.

In his 1962 “We choose to go to the Moon” speech at Rice University in Houston, President John F. Kennedy talked about the need for the nation to accelerate space exploration efforts (1). At the time, the United States was racing to catch up in a space race with the Soviet Union.

On July 20, 1969, the US crossed the finish line first. On subsequent missions to the Moon, astronauts stayed longer and conducted more sophisticated experiments. But public interest lagged; going to the Moon was no longer an achievement. Later manned missions to the International Space Station (ISS) and unmanned missions to other corners of the universe generated valuable information but did not reach the prominence of Apollo 11. As the novelty of space exploration wore off, funding dried up. In recent years, the private sector has entered the race for the commercialization of space.

Space exploration, however, generated scientific benefits and practical applications beyond the spectacle of the Moon walks. A less-publicized statement in Kennedy’s 1962 speech described the prospects: “The growth of our science and education will be enriched by new knowledge of our universe and environment, by new techniques of learning and mapping and observation, by new tools and computers for industry, medicine, the home as well as the school,” he said.

The ISS, an orbiting laboratory 248 miles above Earth, functions as “an unparalleled opportunity to investigate how gravity and the extreme environment of space influence observations in the physical and life sciences—exploiting these effects to understand basic phenomena and advance commercial pursuits” (2).

The ISS website describes how studies of the effects of spaceflight on living organisms will enable scientists to learn more about biology, medicine, and biotechnology and, in turn, advance pharmaceutical development. The laboratory also has unique features not found on Earth. Microgravity causes changes in gene expression, DNA regulation, cellular function and physiology, and 3D aggregation of cells. It also affects fluid dynamics, allowing improved growth of protein crystals and optimization of nanofluidics systems (3). Implementation partners serve as payload developers, preparing research studies for deployment in space.

Life-sciences experiments conducted on the ISS include protein crystallization studies to improve drug design; cell culture experiments to study osteoporosis and immunodeficiency; stem cell experiments for cardiovascular disease; fluid dynamics studies for diagnostics and drug delivery systems; and model-organism research to explore potential repurposing of existing drugs for other uses.

The journey to the Moon demonstrated man’s capabilities to innovate. The ongoing benefits of an orbiting research lab are a testimony to that legacy.

References
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The continued surge in research and development of cell and gene therapies is prompting FDA officials to ramp up guidance development, streamline oversight, and take steps to advance manufacturing and clinical development of these cutting-edge treatments. This wave of innovation includes somatic cell gene therapies able to correct gene defects by replacing, repairing, or inactivating a gene, either by directly administered gene therapy to the patient or by taking cells from the body, modifying them in culture, and returning them to the patient.

FDA’s Center for Biologics Evaluation and Research (CBER) has seen an “explosion” of growth in the cellular and gene therapy area, observed CBER Deputy Director Celia Witten at the Cell & Gene Therapy Products Symposium in June 2019 sponsored by CASSS (1). CBER’s Office of Tissues and Advanced Therapies (OTAT) received more than 400 investigational new drug applications (INDs) in 2018, many qualifying for breakthrough therapy status and the Regenerative Medicine Advanced Therapies (RMATs) designation for products that provide evidence of intent to treat, modify, or cure a serious or life-threatening disease or condition. For such therapies, FDA offers manufacturers extra assistance in developing innovative product testing and production methods, expedited review, and flexibility in documenting quality and meeting requirements.

A main FDA challenge is to devise standards for this burgeoning cadre of experimental products. FDA is working with the National Institute for Standards and Technology (NIST) and has contracted with the Nexight Group to coordinate the standard development and assessment process (2). Collaborations seek standard practices in cell counting, measuring flow cytometry, and assuring cell viability. FDA also is engaged in devising common regulatory approaches and policies for developing and testing innovative therapies with authorities in other regions. The Gene Therapy Working Group of the International Pharmaceutical Regulators Programme (IPRP) has finalized a reflection paper on expectations for biodistribution assessments for gene therapy products (3). This may provide a basis for the International Council for Harmonization (ICH) to develop a guideline on biodistribution studies of gene therapy vectors (4).

FDA may exercise flexibility on the extent of manufacturing information in submissions.

A main challenge in testing and developing these new therapies, Witten noted, is to devise new tools and policies to support more complex manufacturing processes. A lack of capacity for producing lentiviral and adeno-associated virus (AAV) vectors can limit clinical development, she observed, while current cell lines often are not able to meet demand for large-scale or rapid production. Regulators and sponsors are looking to advanced manufacturing technology devised for vaccine production processes to inform similar approaches for optimizing cell lines for production, improving yield of recombinant technology, and applying continuous manufacturing concepts to new treatments.
The expedited development and approval of cellular and gene therapies requires a “new paradigm,” said Steven Oh, deputy director of OTAT’s Division of Cellular and Gene Therapies, at the CASSS symposium. He noted the unique challenges created by limited manufacturing experience prior to licensure and limited understanding of critical quality attributes (CQAs) due to difficulties in characterizing the drug product, drug substance, and in-process material for these therapies. Products vary, moreover, due to unusual source materials, less qualified assays, and limited stability data.

Despite these difficulties, Oh emphasized that sponsors cannot ignore requirements for complying with chemistry, manufacturing, and controls (CMC) and current good manufacturing practice (cGMP) standards. It is important, therefore, to focus on these issues early in clinical development to support the accelerated review and approval of a product with a breakthrough or RMAT designation. Manufacturers should plan for commercial-scale manufacturing and conduct needed comparability studies as early as Phase I and II studies. Raw material qualification and supply chain issues should be addressed, and assays should be developed and validated.

At the same time, FDA may exercise some flexibility on the type and extent of manufacturing information expected with a submission, particularly for validation strategies and the manufacturing scale-up program, Oh said. He added that such leeway will depend on product characteristics, the seriousness of the condition being treated, the type of manufacturing process, the robustness of a quality system, and the strength of the risk-based quality assessment. Regulatory flexibility usually will be linked to agreements on post-marketing commitments and requirements.

To assist manufacturers in designing untraditional production or development programs, CBER officials have established the CBER Advanced Technologies Team (CATT) to discuss and respond to queries from industry on advanced manufacturing and testing technologies (S). This team aims to assist in developing products where CBER has “limited experience with the manufacturing or development process.” CBER wants inquiries to briefly describe the technology, why it is novel and unique, its potential impact on product quality, and a summary of the manufacturing or development plan.

Developers of innovative therapies similarly can use CBER’s INTERACT program (INInitial Targeted Engagement for Regulatory Advice on CBER producTs). This replaces pre-pre-IND interactions and offers early-stage informal consultation on product development. INTERACT is particularly useful for complex or novel manufacturing technologies, innovative devices, and cutting-edge testing methodologies. Such early discussion provides non-binding advice and doesn’t replace the recommended pre-IND meeting for products further along the development pathway.

A CBER internal working group on advanced manufacturing is soliciting proposals to support innovation relevant to producing complex biologics, including novel and improved materials, manufacturing innovations, and new analytical methods. CBER is expanding laboratory research programs and collaborating with academics and other partners to develop improved cell lines for vector production and advanced manufacturing technologies.

These strategies to provide appropriate and efficient pathways for bringing innovative therapies to patients so far have involved treatments for single-gene disorders that generally affect very small patient populations. The challenges will increase as more manufacturers propose remedies for multigenic targets, such as Parkinson’s disease, which will involve new approaches for clinical trials and for production scale-up.

REFERENCES
Industrializing Cell and Gene Therapies

Now that the first genetically modified cell therapies are being manufactured, the industry must move beyond “whatever works” to meet growing demand.

AGNES SHANLEY

In less than four decades, biopharmaceutical manufacturing has traveled light years from its origins in facilities such as Amgen’s Building Six in Thousand Oaks, California, which manufactured 200 grams of recombinant human erythropoietin per year with two stainless steel tanks and 3000 roller bottles (1). As increasingly sophisticated equipment was developed for upstream and downstream processing, standardization allowed for the engineering of new processes and platforms and faster development and scale-up.

Cell therapies, genetically modified cell therapies, gene therapies, and tissue engineering now stand where biotech was in the late 1980s; the first products have been commercialized and manufacturing them has become a question of doing whatever works.

“The greatest success so far has been the fact that the industry has even launched the cell and gene therapy products that it has introduced. Regulators have accepted them, and developers have figured out how to get them to the market,” says Phil Vanek, general manager of cell and gene therapy strategy, GE Healthcare.

The next phases of industrial development, Vanek says, will focus on streamlining the supply chain and the creation of increased therapeutic value; engineering new therapeutic value into the cells to achieve the highest potency per amount of production time and cost; and connecting both of these efforts, via an intricate pathway, directly to patients.

“We must draw on the valuable experience that we acquired in biologics manufacturing, where we evolved from small to large volumes and from stainless-steel to single-use platforms for flexibility,” says Lisa Krallis, head of business development, cell and gene technologies at Lonza Pharma & Biotech.

THE PRESSURE IS ON

As the cell and gene therapy market grows, substantial pressure is on developers to meet commercial demand and supply clinical quantities of material. By the end of 2018, 1028 global clinical trials were underway for cell and gene therapies, 58% of them for oncology therapies; 57% of them in Phase II, and nearly 9% in Phase III, according to the Alliance for Regenerative Medicine’s 2018 Regenerative Medicine Data Report (2). That year, more than 906 companies focused on cell and gene therapies, generating $19 billion in merger and acquisition activity and $13.3 billion in corporate financing for research and development, up 73% from 2017.

Meeting increased demand will require a one-to-two-orders-of-magnitude improvement in gene therapy vector manufacturing, and a similar reduction in cost, as Peter Marks, director of
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FDA’s Center for Biologics Evaluation and Research noted at the 2018 Galien Foundation’s Forum (3). “Platforms need to become standardized, industrialized for yield, and then optimized for complexity,” says Krallis.

MANUFACTURING PLATFORMS

Today, efforts focus on improving existing manufacturing platforms for both patient-specific, or autologous therapies, and allogeneic treatments designed for many patients (4). They include in-vivo adeno-associated viral vector (AVV) technology, which enabled the commercialization of Spark Therapeutics’ retinal blindness therapy, Luxturna, which FDA approved in December 2017. Roche plans to acquire the company (pending approval by the US Federal Trade Commission) (5).

Also being developed are ex-vivo Lentivirus vectors, which modify cells that have been removed from a patient, then are combined with T or stem cells and injected back into the patient, an approach that Bluebird Bio is using for chimeric antigen receptor (CAR)-T cell therapies (3).

Novartis and Kite have developed faster autologous CAR-T processes, while ZIOPharm is refining its Sleeping Beauty non-viral gene transfer platform, which FDA approved for use in T-cell receptor cell therapy in June 2019 (6). That same month, FDA approved the first clinical trials using UCART123, an off-the-shelf, allogeneic cell therapy approach developed by the French company, Cellectis (7) that uses Talen, a proprietary gene editing technology. Trials are already underway for UCART19 and UCART123, other therapies that utilize the technology.

“With queues for new vector production frequently around 12 months, the industry isn’t where it needs to be in terms of production capacity,” says Andrew Bulpin, head of process systems at MilliporeSigma. “As a result, innovation focuses on improving scalability to enhance the amount of material produced per run.” Upstream, the best way to improve scalability is to move cell culture into suspension. “Current vector production is disproportionately done in adherent culture, which is only conducive to scaling out, not scaling up. There is also significant use of serum in cell culture media, which increases regulatory burden and creates a potential supply bottleneck,” says Bulpin. Moving culture into single-use bioreactors improves scalability and enables a shift to chemically defined media, solving a number of problems at once, he says.

For downstream processing, Bulpin explains, the picture is more complex because of the number of steps required in the workflow. “In addition to process complexity, there is a need to increase the scale that current unit operations can handle as well as to minimize the loss of vector in each unit operation. Innovations in chromatography and filtration will be important to achieving those goals,” he says.

EQUIPMENT DESIGN

Platforms specifically designed for viral gene therapy applications could address more of these challenges at once and will be essential for ongoing growth in the industry, says Bulpin. At this point, innovative therapies are still being developed in equipment that was designed for traditional biopharmaceuticals, and there is a disconnect. “In biologics, the cell is a byproduct, and material is purified by removing that byproduct,” explains Vanek. “In cell therapy, however, the cell is the final product, so we must be very careful to develop platforms and approaches that do not fundamentally change the biology of the cell. That’s a tall order,” he says.

As more is learned about innovative therapies in the clinic, equipment will eventually be customized for use with cell and gene therapies, Vanek says. “Every cell type will have a set of specific conditions that it thrives under, and those conditions will ultimately be developed into next-generation equipment, whether bioreactors, cell processing platforms, and ancillary materials, upstream and downstream methodologies, including everything from reagents to hardware, to consumables and software,” he says.

ALLOGENEIC VS. AUTOLOGOUS NEEDS

“In patient-specific therapies, you may not need more than a billion cells per batch, but if you start to scale up in allogeneic you might need hundreds of billions of cells per batch,” Vanek says. In order to scale up and increase the volumes of allogeneic cell therapies, manufacturers will need to be able to move seamlessly from adherent to suspension cell culture, says Krallis, and ultimately 2000 L single-use bioreactors of the type now used for viral vectors may be needed for allogeneic applications to achieve the required cell volumes.

“Suspension processes for allogeneic manufacturing have been established for some time, so there has been more work adapting processes for these needs than there has been for vector production,” says Bulpin. Closed, automated technology platforms will be critical in the future, he says.

Autologous therapy development will not be one size fits all, says Krallis, who emphasizes the need for “mass customization,” which she defines as “automating processes while remaining flexible from the clinical-to-commercial phase and adapting to the quality of the raw material.” Lonza launched its closed, automated Cocoon platform (acquired via its purchase of Octane Biotech in 2018), which aims to help developers achieve this goal and is currently being used by Sheba Medical Center to produce autologous therapies (8).

AUTOMATION AND DIGITIZATION

Although most biopharmaceutical companies are adopting automation, cell and gene therapies pose challenges, says Bulpin. “Unlike monoclonal antibodies that utilize robust and predictable immortalized cell lines, CAR-T therapy requires the patient’s own cells for further processing. Incoming cell composition from patient to patient is exceedingly variable. Automation and process control for CAR-T manufacturing will require a high degree of flexibility for variable cell inputs while also providing robust and predictive processing,” Bulpin says.
Data management will also be crucial for autologous manufacturing, which will require patient tracking to ensure that the product makes its way back to the intended recipient. “It is also extremely important, given that many of these patients have not responded to chemotherapy and radiation therapy, that the manufacturing process be short and patient scheduling seamless,” Bulpin says.

As he notes, the typical CAR-T manufacturing process can take anywhere from 20–30 days, with a significant portion of this time dedicated to release testing. Bulpin suggests that using in-line sensors for real-time quality control release testing could improve overall efficiency.

“To support this new type of manufacturing, we are going to need to replace as many manual processes as possible with closed and automated processes, so the labs will look very different as a result,” Krallis says. In addition, she sees the need for a new digital approach to managing manufacturing systems. “Especially as we increase the number of patients treated per week with autologous cell and gene therapies, it is key to have the right data-management systems in your manufacturing setup to track and trace all patient material in real-time, before, during, and after manufacturing,” she says.

Vanek agrees that digitalizing the overall process will be crucial to development of personalized medicine. “If you’re translating from a clinic and you have a therapeutic that’s progressing through clinical trials, there is a need for better data management and integration. Even at the unit operation level or the individual step of a larger process, just being able to connect data in a cohesive fashion is crucial,” he says.

DIGITALIZING TO IMPROVE MANUFACTURING

Although many pharmaceutical companies are at a very early stage of digitalization, Vanek believes that capabilities can be adopted sequentially. The first step would involve connecting data with batch records and standard operating procedures (SOPs) so that the information becomes part of the manufacturing record. GE launched a platform called Chronicle in May 2019 (9) to enable e-notebook and e-SOP connection in a more streamlined way, he says.

“You must think of this from the beginning and connect and coordinate data from the quality control release testing efforts and the quality assurance and regulatory affairs teams that are ultimately responsible for the quality of that product.”

But he acknowledges that this is only the first level of integration. Data must flow from the patient through the manufacturing process and then back to the patient, and all the elements of the complex supply chain must be coordinated, he explains, so the second level of digital integration will connect digital patient records, the materials flowing in, as well as the production process into one manufacturing workflow.

“Ultimately, you want to escalate that integration to the point where it’s part of a manufacturing execution system (MES), to start to schedule, coordinate, and orchestrate all the moving parts. This will require a much more sophisticated capability than the industry has today,” Vanek says.

FACING CHALLENGES

Beyond digitization and automation, developers face a number of other challenges as they scale-up cell and gene therapies. One concern that Krallis notes is requirements for and availability of the complex raw materials (e.g., plasmids and lentivirus) required for manufacturing. In addition, she says, as the field evolves, developers must be careful about investing too-much too-soon in technologies that may soon be outdated, before they recover their capital expenditures, she says.

Ultimately, she says, developers face reimbursement challenges and the need to balance cost effectiveness in the scaled-up process with demands to reduce drug cost to patients. She believes that contract development and manufacturing organizations (CDMOs) can offer developers a way to control operating and capital costs, allowing them to focus on pipeline development.

Bulpin sees the shift toward personalized, point-of-care medicine as a challenge for the delivery of finished therapies. Another hurdle is the long timeline from development through manufacturing, he says.

As more companies get involved in personalized medicine development, all stakeholders including operating companies, CDMOs, technology vendors, and research organizations are forming alliances to stay ahead of challenges and share different perspectives. One example is the Centre for Advanced Therapeutic Cell Technologies in Toronto, Canada, whose members include GE Healthcare and the NJII Cell and Gene Therapy Development Center, which works with Pall Corp.

The dynamics of collaborations in this field may differ from those in traditional biopharmaceutical development. One reason is the complexity of the supply chain, especially for autologous therapies, because the starting material is the patient’s own cells, says Bulpin. “Closed and automated systems offer the potential for manufacturing sites to be located closer to the patient, regionally or even at the hospital. In this context, CDMOs may require satellite facilities, or academic medical centers may take on more of a CDMO role,” he says.

Another difference from traditional biopharma is the fact that many of the therapies originated from research and discovery conducted by the doctors and academics at hospitals and research institutes, says Krallis. “Institutes can manufacture therapies for clinical trials but most of them don’t have the expertise or the capacity to make product at commercial scale. Instead, the therapies get spun off to new companies and are usually tech-transferred to a CDMO,” she says, noting that CDMOs

Continues on page 46
Monitoring and Control of Inline Dilution Processes

Successful process intensification with inline dilution requires effective monitoring and control.

CYNTHIA A. CHALLENER

Process intensification is a major focus of the biopharma industry, with most efforts targeting upstream cell culture and associated processes. Buffer management has received less attention, despite the high costs and labor-, space-, time-, and material-intensive nature of this common downstream activity. Inline dilution (ILD) combined with inline conditioning (IC) is one of the key ways to intensify downstream processes, according to Avril Vermunt, program manager for connected biomanufacturing at GE Healthcare Life Sciences.

Large tank farms in biomanufacturing plants occupy expensive real estate that can be put to more productive use in today’s drive to intensify the production environment, agrees Gerard Gach, chief marketing officer for the Bio/Pharma Systems Group of YMC Process Technologies. “The advent of buffer concentrates delivered in single-use (SU) bags combined with automated, compact precision dilution and blending technology allows these tank farms to be repurposed for more productive activities,” he says.

Large tank farms in biomanufacturing plants occupy expensive real estate that can be put to more productive use in today’s drive to intensify the production environment, agrees Gerard Gach, chief marketing officer for the Bio/Pharma Systems Group of YMC Process Technologies. “The advent of buffer concentrates delivered in single-use (SU) bags combined with automated, compact precision dilution and blending technology allows these tank farms to be repurposed for more productive activities,” he says.

Using concentrated buffer recipes for ILD, or individual buffer component stock solutions that are blended, titrated, and adjusted with IC, it is possible to provide the needed process stream.

According to Vermunt, using ILD and IC, GE has shown that the volume of buffer hold tanks can be reduced up to 90% and the total footprint reduced by 40% compared with manual buffer preparation. “Automated buffer preparation methods can lead to a more efficient use of existing resources, including labor and consumable savings, and smaller facility footprints. Eventually, by getting more out from their existing facilities, biomanufacturers can avoid or delay substantial capital investments,” she states.

In addition to freeing up space, optimizing labor, and improving operator safety, these systems can be programmed for use with existing buffers or supplied as end-to-end solutions with concentrates and SU tubing and bag sets, according to Gach.

SECRET OF SUCCESS

This first step in establishing a successful inline dilution solution is to determine the right buffer management approach for the manufacturing facility and process as early as possible. “This assessment tends to take place late, and biomanufacturers...”

CYNTHIA A. CHALLENER, PhD, is a contributing editor to BioPharm International.
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are still choosing manual buffer preparation because there is not much time invested in looking at alternatives such as automated solutions and outsourced buffers,” Vermunt observes.

An effective evaluation will include investigation of the total cost of ownership, including space requirements, future expansion plans, labor costs, and quality control, among other factors. “It can be challenging to complete this type of comprehensive assessment, but it helps to understand how resource-heavy buffer preparation really is beyond the straightforward material costs,” comments Vermunt.

Successful implementation of automated solution like IC and ILD then requires selection of the design option best suited for the specific process needs, considering the number of buffers to be used and their concentrations and flow rates. “It is important to compare the different alternatives and understand the pros and cons of each before making the final decision,” Vermunt says. The buffer control strategies must also be understood. She also notes that it is important to recognize that while the upfront costs of ILD are greater, one of the biggest drivers for these solutions is long-term cost savings.

The use of proven technology combined with on-site support and confident buy in from the quality assurance team responsible for buffer quality also contribute greatly to successful implementation, according to Gach. “On-site expert support is an important factor. The systems we supply are pretty much plug-and-play; however, the on-site availability of a vendor with the production site process engineers and operators adds a significant degree of implementation security,” he observes.

**MONITORING AND CONTROL**

When looking at the buffer preparation process, the target product profile should be defined first followed by critical quality attributes and critical process parameters, which finally leads to the optimal control strategy. “Typically,” says Vermunt, “each buffer is defined by critical process parameters essential for the process, including pH, conductivity, temperature, and buffer component concentration or molarity. To ensure robust performance, system blending, flow control, and monitoring of critical parameters must be considered,” she asserts.

Another important factor for consideration, according to Vermunt, is the fact that for many buffers, creating a concentrate suitable for ILD is equal to the study and characterization needed for use-strength buffers. “The natural tendency is to assume that a component’s recipe in a concentrate is proportional to the diluted amount. However, especially for a use-strength buffer, which is close to the buffering system’s pKa, the effects of water and dilution can shift the pH,” she explains. This issue must also be considered when ILD is used for chromatography and pH is a key operating parameter. In these cases, concentrate recipes should be characterized to consider the potential pH shift.

**SELECTING A STRATEGY**

A potential deviation during inline buffer dilution can risk the product quality or yield. When choosing a control solution, therefore, it is critical to consider what risk level is acceptable, according to Vermunt.

While quality control of the incoming concentrates adds a degree of certainty to the blend outcome, paramount is a feedback control that does not drift over time or require regular re-calibration, Gach asserts. “YMC recommends volumetric flow control with pH and/or conductivity monitoring.” Volumetric flow control for blending of buffer constituents, he notes, provides superior, reproducible, buffer composition, and accurate dilution because flow control is less prone to measurement drift than chemical sensors such as pH and conductivity. In addition, pH and conductivity require frequent calibration.

“While our system is also capable of pH and/or conductivity control to adjust the flow rate of the buffer concentrate or diluent based on pre-defined pH/conductivity set points, we have found over many years and numerous installations that this method is not our recommendation for primary control of the dilution process due to the delay in feedback control and potential for these devices to drift over time,” comments Gach. “YMC systems also have an automated function to send to waste or recycle a dilution that may deviate from a customer pre-set band of pH or conductivity, assuring the final buffer falls within the customer’s quality set point.”

GE Healthcare Life Sciences’ manufacturing-scale systems are typically equipped with three options for ILD control: open-loop flow ratio control, flow feedback control, or conductivity feedback control. All include monitoring of pH, conductivity, or flow to confirm the buffers are in range. “There is no one recommended way to go as all three options have their benefits and challenges,” Vermunt says. For example, open loop is a cheaper option, and it has the simplest design. But if the pH or conductivity goes out of specification, the ratio will not automatically adjust as with inline feedback control.

Accurate blending is also important, according to Gach. He notes that metering pumps, particularly those that are servo controlled, more accurately and consistently blend buffer constituents to the exact molecular ratio that was defined in the original process qualification at the lab scale.

For more advanced control, IC is an option, according to Vermunt, because it enables additional feedback options including pH and pH/conductivity feedback as well as adjustments appropriate for working with corresponding acids and bases or strong-weak interactions.

**AUTOMATED SOLUTIONS**

Advances in automated ILD solutions continued to occur. “Automated systems that provide highly precise and reproducible buffer dilution are available...
LOGICAL NEXT STEPS

Vendors of ILD systems such as GE Healthcare Life Sciences and YMC Process Technologies are not resting on their laurels, however. Demands for process intensification continue to evolve, and advances in technology must occur in tandem. For instance, Vermunt notes that for years there has been a limitation to implementing ILD in SU systems due to a lack of suitable disposable pump and flow sensor technologies. “Today there are new SU pump and flow meter options available that are better-suited to provide ILD. GE has begun to incorporate them into our next-generation SU systems, and we will continue to evaluate new instrumentation for our systems to ensure performance and flexibility,” she says.

Documentation is another area that is evolving, according to Gach. “Linking the concentrate quality documentation to the hardware control/recipe generation and paperless final quality record would be a logical next step. This documentation linked to the buffer dilution system on-board control would further increase quality and reduce cost,” he observes.

IC RECIPES AND FLOW

In addition to ILD, IC is gaining popularity in the industry mainly due to the additional flexibility and benefits that can be achieved in manufacturing, according to Vermunt. “The system uses different buffer families in one production run to provide all the buffer formulations, affording a high degree of flexibility. Importantly, with IC it is possible to select the feedback mode that best controls the buffer critical process parameters and ensures mass balance,” she adds.

For IC systems, the dynamic control functionality are recipe and flow; pH and conductivity. With recipe and flow feedback, a known buffer formulation is entered in the system control software, which adjusts the flow rates of the specified stock solutions to achieve the desired formulation. This control mode is useful when the temperature is constant and the stock solutions are accurate.

With pH and flow feedback, the user enters the target pH and the software adjusts the flow rates of the acid and base stock solutions to achieve the desired pH in the final formulation. With pH and conductivity feedback, after the user enters the target pH and conductivity, the dynamic control functionality of the software uses the feedback from flow, conductivity, and pH sensors to adjust the flow rates of the stock solutions to achieve the desired conductivity and pH. In this control mode, both the temperatures and the concentrations of the stock solutions can vary without affecting the accuracy of the final buffer formulation.

IC systems also have the functionality required to operate as a chromatography unit, allowing direct connection to a chromatography column to make it possible to deliver the buffers directly to the process without the need for storage in bags or tanks, according to Vermunt. Waste is therefore only generated during the switch between buffers until the set pH is reached and stable.

GE has conducted a study to address the need for proof that automated buffer formulation meets specifications. In this study, the IC technology was evaluated from a current good manufacturing practice (cGMP) perspective to answer the question: Can we rely on a machine? The results show, according to Vermunt, that automated solutions like inline conditioning can be successfully implemented if the critical process parameters, in this case pH, conductivity, and buffer concentration, are kept under control. The hardware, software algorithms, and chemistry also must work seamlessly together.

“Implementing technologies such as ILD and IC helps streamline the entire buffer preparation process and reduces manual handling by automating several steps, not only reducing the risk of human errors, but also making it possible to reassign personnel to other tasks that provide more value,” Vermunt concludes.
Gene-editing methods such as clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 are used for disease research; clinical studies using the method are ongoing. A growing use of CRISPR-Cas9 and other gene-editing techniques to modify the genetic makeup of mammalian-based cells, such as Chinese hamster ovary (CHO) cells, is used for therapeutic antibody production.

To explore the role gene-editing techniques can play in regenerative medicine and cell-line development, BioPharm International interviewed Lise Munsie, senior development manager at CCRM, a Toronto, Canada-based not-for-profit consortium that supports the development and commercialization of cell and gene therapies and regenerative medicine-based technologies, and Kevin Gamber, vice-president of Canopy Biosciences, a St. Louis, MO-based life-sciences company that offers tools and services for gene editing and bioprocessing applications.

Application of gene-editing tools
BioPharm: What is the most commonly used genome-editing tool today? How has this tool impacted the development of cell lines for use in therapeutic antibody production?

Munsie (CCRM): Although CCRM does not currently make therapeutic antibodies, the ability of CRISPR-Cas9 to easily manipulate the genome of antibody producing cells, such as CHO cells, to enhance antibody production would be game-changing. Scientists can easily alter genes they think are assisting the cells in antibody production, for instance, by manipulating genes that regulate the cell cycle or divert energy from other normal cellular processes towards antibody production. Prior to CRISPR-Cas9, this [manipulation] would have been too cumbersome to do in an efficient and relevant manner.

Gamber (Canopy Biosciences): CRISPR-Cas9 has taken the gene editing world by storm. It is more efficient and much easier to design and construct than previous gene-editing tools, such as zinc finger nucleases (ZFNs), [Transcription Activator-Like Effector Nucleases] TALENs, and meganucleases. For therapeutic antibody production, it has been used both for site-specific integration of antibodies for bioproduction as well as to generate better host cells; the development of cells with increased yields, for example.

BioPharm: What other genome-editing tools are predominantly used today by the biopharmaceutical industry for cell-line engineering?

Munsie (CCRM): There are classic tools like ZFNs and TALENs. Scientists are increasingly making modified-Cas9 variants to make them more specific or efficient, and new enzymes that function in a manner similar to Cas are regularly being discovered.

Gamber (Canopy Biosciences): ZFNs are also used. ZFNs have a clearer intellectual property position than CRISPR. Additionally, stable cell lines are still being generated through standard transgenic techniques—transfection of a transgene followed by selection.

Pitfalls and potential
BioPharm: What are potential pitfalls or disadvantages of using a genome-editing tool to custom engineer CHO cells?

Gamber (Canopy Biosciences): The off-target effects generated by CRISPR-Cas9 have been well documented. Off-target effects occur when the gene editing tool makes unintended edits to other genes in addition to the target gene. Off-target editing is not species specific. Off-target effects can be largely mitigated through careful design of the reagents.

BioPharm: Will genome-editing technologies continue to play a significant role in customizing cell-line development, or are other technological tools expected to break through?

Munsie (CCRM): Gene editing is still in its infancy and will continue to be a major player in the cell-line engineering field for a long time to come.

Gamber (Canopy Biosciences): Gene editing via CRISPR-Cas9 will continue to be an extremely important tool for gene editing. Improvements on the technology are continuing to be made, as well as alternate systems being identified. Therapeutic use of CRISPR-Cas9 technology, such as Chimeric antigen receptor T cells as immunotherapy for cancer, will increase in use and hopefully become a powerful new approach to a wide variety of diseases.

BioPharm: What needs remain unmet in biologic drug engineering/development, and can genome-editing tools address these unmet needs?

Munsie (CCRM): Most regenerative medicines rely on autologous stem cell sources due to the immune response that occurs when allogeneic cells are introduced into a person. However, there is a lot of interest in using CRISPR-Cas9 to manipulate allogeneic cells and knock-out proteins that signal the immune system. These cells could then be used in multiple donors for many different therapies without the issue of rejection. Additionally, genome-editing can be used to knock-in genes. In the case of universal cells, it would be desirable to knock-in an exogenous gene that could be used as a kill switch in the event your regenerative medicine therapy had ill-intended effects.

“The editors of BioPharm International
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Enhancing Cell Harvest

Higher cell densities are driving innovations in harvesting, including closed systems for intensified processes.

JENNIFER MARKARIAN

The cell harvest step prepares a clarified, sterile feedstream for downstream purification. The trend toward higher cell densities and the resulting higher biomass coming from the bioreactor create additional challenges for the harvest step, but suppliers aim to meet this and other challenges with various technologies that improve process efficiency.

Process robustness and capacity and throughput issues are a challenge, says Vincent Pizzi, BioProcess Upstream strategy leader, GE Healthcare. “Legacy harvest technologies using depth filtration or centrifugation followed by depth filtration have approached this challenge of higher density cell-culture feeds by increasing cycle times or filter area. These approaches have [negatively] impacted the industry process economics and workflow efficiency. Other challenges are the extensive use of water for injection and handling of filter modules with larger volumes,” explains Pizzi.

Madhu Raghunathan, product strategy manager at GE Healthcare, sees increased acceptance and adoption of concentrated fed batch (CFB) and continuous perfusion using tangential flow filtration (TFF) or alternating tangential flow filtration (ATF) for the cell-culture step. “With continuous perfusion, the use of a cell retention device (TFF/ATF) enables direct loading of the product onto the capture chromatography column, bypassing the harvest-clarification steps. However, it is important to choose the correct cell retention device and framework to eliminate and minimize membrane fouling, and to avoid making the perfusion step onerous and labor-intensive,” says Raghunathan.

He says that CFB commonly generates final cell densities greater than 50 million cells/mL, which results in a need for improved harvesting technologies. “At that final density, depth filtration becomes less effective in terms of filtration capacity in liters processed per depth area. Here we see users evaluating the implementation of newer technologies for harvest clarification, such as adding diatomaceous earth to reactors, pH shifts, flocculation, or acoustic separation, among others. These technologies also have challenges, such as the scalability along with system footprint, the need to prove removal of flocculants, and the impact on ion-exchange chromatography steps, for instance.”

Acoustic wave separation enables the continuous removal of cells and cell debris for either batch or continuous bioprocesses. “Pall’s Cadence Acoustic Separator retains recirculating cells from a perfusion bioreactor without the need for a hollow fiber filter device. Having no membrane means no fouling or loss of product, and results have shown simplified integration of the cell retention technology with perfusion bioreactors at cell densities of up to...
100 million cells/mL with 100% product transmission under typical process conditions used in the continuous production of biologics,” says Peter Levison, executive director of business development at Pall.

John Bonham-Carter, product line leader for Repligen’s Cell Culture & Clarification Business, says that the company’s XCell Alternating Tangential Flow (XCell ATF) equipment has become an industry standard for cell retention in perfusion and intensified fed batch cultures. “The key advantages are enabling a hollow fiber filter to be used for longer without either cells blocking flow in the lumens or blocking of the filter pores, restricting product harvest. ATF delivers a backflush across the lumen, keeping the pores cleaner, and also flushing cells back to the reactor every 5–10 seconds, [thus] inhibiting blockages,” he explains. “The XCell ATF is used in a N-1 perfusion step in multiple 12–20-kL stainless-steel facilities across the world for several commercial therapies. Additionally, for smaller clinical facilities or for gene therapy manufacturing, the XCell devices are the go-to product for boosting productivity via N-1 perfusion.”

Biopharmaceutical manufacturers are seeking further innovations in cell harvest to improve efficiency. “The variation in cell culture feed experienced in harvesting means titers and yield can be variable, and often more depth filters than might be required are used as a safety factor. As always, people would also like to save time, both on preparation and maintenance of equipment and during the operation of the process step,” says Bonham-Carter.

**HIGH-PRODUCTIVITY HARVEST**

Repligen has been promoting a relatively new method—high-productivity harvest (HPH) using the company’s XCell ATF equipment—to improve harvest for fed-batch processes. Using ATF eliminates the need for a centrifuge, and it operates as a closed, sterile system. “The HPH method makes a few other changes to reduce impurity build-up and boost protein production. Since the harvest is clarified, no depth filters are required either,” explains Bonham-Carter. He says that Repligen developed the process over several years and is now optimizing and adapting it with interested customers.

Bonham-Carter explains how HPH works: “The sterilized XCell device is attached to the bioreactor in an aseptic manner to keep a closed system. A diafiltration process is started a day or more earlier than at typical harvest, and product starts to be harvested immediately at a slow rate. The media diafiltration has the benefit of keeping cells more viable and so avoiding creation of host cell proteins and other contaminants or byproducts. [Diafiltration also] minimizes degradation of the target protein. On the final day of the fed-batch process, the diafiltration is stopped and the harvest is speeded up, emptying the reactor through the 0.2-micrometer polyethersulfone filter. Depending on initial and final cell concentration, a small diafiltration may be appropriate towards the end of the run, but typically yields are already in excess of 100%, which minimizes the need for complexity or further dilution.”

The yield boost is significant, says Bonham-Carter, and typically 120% to 200% yield is expected. HPH can be used for higher yield (i.e., more protein in the same period of time), or it can be used for faster yield (i.e., harvest earlier to increase throughput). This decision should be balanced with the cost of media, because more media is needed if throughput is higher, notes Bonham-Carter.

HPH is scalable, adds Bonham-Carter. For example, one ATF-10 is running in a GMP facility with a 2000-L bioreactor using fed-batch. A 5000-L fed batch system could use two ATF-10s, he explains.

The XCell ATF is available as either a stainless-steel or single-use system, both of which use a single-use hollow fiber for filtration. “A steel version is often preferred for those people who already have an investment in a large steel facility equipped with steam lines and an autoclave, and those people who expect to run hundreds of batches per year,” says Bonham-Carter. “Single-use devices are preferred by those who don’t have an autoclave, need flexibility and fast start-up/shut down, and run in multi-product facilities.”

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**Separating microcarrier beads**

Separating microcarrier beads used during adherent cell production is another challenge for cell harvest. “Current techniques require significant capital, routine maintenance, an open system and long cycle times, and could potentially yield low recovery rates,” says Jarv Campbell, senior product manager, Single Use Technologies, Thermo Fisher Scientific. The company’s single-use Harvestainer Microcarrier Separation System was designed to separate microcarrier beads from the cell debris and virus found in the cell culture supernatant in a single-step, closed system that reduces cross-contamination concerns while maintaining high yields, says Campbell.

The system is available in multiple sizes. The 3-L and 12-L Harvestainer systems consist of a preassembled 2D bioprocess container (BPC) and tray that acts as the secondary containment device. The 25-L and 50-L systems consist of a 200-L 3D BPC with a drum as the secondary containment device.
The Case for Stainless Steel

Despite the growing popularity of single-use technologies in biomanufacturing, there are still instances where stainless steel is the better option.

SUSAN Haigney

Single-use technologies are becoming increasingly popular in biomanufacturing. What does this mean for the fate of stainless-steel equipment, especially in commercial biomanufacturing? According to Brady Cole, ABEC vice-president, Equipment Solutions, stainless steel will be around for some time.

The continued use of stainless steel will be maintained by the process and output requirements of biopharmaceutical manufacturing, says Arleen Paulino, senior vice-president, Manufacturing at Amgen.

Parrish M. Galliher, CTO Upstream and founder, Xcellerex Inc., GE Healthcare Life Sciences, agrees. “As long as we are trying to develop more universal blockbusters such as treatments for cancer, inflammation, diabetes, dementia/Alzheimer’s, these will likely require very large annual capacities.”

When it comes to producing large volumes of product, the use of stainless-steel equipment saves money and fills gaps in the capabilities of single-use equipment, says Andrew Bulpin, head of Process Solutions at MilliporeSigma. “For instance, maximum flow rates in single-use technologies are not at par with stainless-steel. Manufacturers will also continue to leverage existing facilities and inherent expertise at these sites to manufacture new therapies. While we often focus on mAb [monoclonal antibody] production, the plasma and vaccine industries are likely to continue adoption of hybrid facilities where stainless steel carries out many core purification operations, but single-use can increase flexibility and efficiency in the bioreactor and fluid management operations,” says Bulpin.

*BioPharm International* spoke with Cole, Bulpin, Galliher, and Paulino about the areas where single-use may not yet venture and where traditional stainless steel is required.

**THE CONTINUED NEED FOR STAINLESS STEEL**

**BioPharm:** In what instances are stainless-steel bioreactors the better, or more appropriate, choice to use over single-use bioreactors?

**Cole (ABEC):** We view the stainless steel/single-use bioreactor choice for commercial manufacturing to be case-by-case based on multiple factors, including cost of goods targets, process requirements, capital/operating cost considerations, validation/regulatory aspects, number of products to be produced in the facility, production quantities needed,
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and the development and manufacturing history of the product. As a provider of both types of bioreactors, we are assisting manufacturers with this decision in an unbiased manner. Some general trends favoring single-use include multi-product facilities, lower production quantities needed, and higher titer products, but even these are not absolute, and we see continued viability of stainless steel for many applications.

**Paulino (Amgen):** There are multiple factors where a stainless-steel bioreactor could be chosen over a single-use bioreactor. As an example, certain manufacturing processes may not work well in single-use bioreactors and, therefore, the option of using stainless-steel bioreactors will be required. Another factor could also be the required output over time coupled with titers of a given process (i.e., the larger the output and lower the titers, the more likely a stainless-steel bioreactor may be chosen).

**Galliher (GE Healthcare):** Stainless-steel bioreactors are more suited for very large-scale manufacturing for drug quantities over 3000 kg/yr. Also, if any non-polar solvents are used or produced by the bioreaction, stainless steel is more resistant to damage by those compounds.

**Bulpin (MilliporeSigma):** Single-use bioreactors (SUBs) have gained traction over stainless-steel bioreactors (SSBs), mainly for early clinical trial phases when process development and process scale-up are occurring and the quantities of cGMP [current good manufacturing practice] drug material are still limited. When flexibility and quick changeover are key assets to move drug candidates forward and eliminate unsuccessful molecules from the pipeline faster, advantages provided by SUBs make a tremendous difference. The emergence of highly potent drug molecules is also playing a key role in the adoption of SUBs because they protect operators from harmful exposure.

Ten years ago, however, I don’t think anyone predicted such massive adoption. SUB providers, regulatory bodies, industry consortia, and—most importantly—drug manufacturers have made tremendous progress to overcome what the industry used to depict as major hurdles for adoption: extractable and leachable data, plastic film robustness, and hardware capabilities, especially with respect to single-use sensors.

Today, upstream process intensification strategies, supported by the increased use of perfusion operations, are carrying SUBs to the next level. Their enhanced sparging and mixing capabilities allow SUBs to support significantly higher cell densities with 60 x 106 cells/mL on average and greater than 100 x 106 cells/mL consistently being reported. Combined with their inherent flexibility, ease of use, and scalability, they can now be used for either high seed fed-batch or steady-state perfusion operations up to a 2000-L scale. Depending on the indication and dosage, the industry can now design fully single-use upstream suites, even at commercial manufacturing scale.

SUBs and SSBs are currently seen as tools in the upstream toolbox to be used appropriately depending on the manufacturing strategy. There are scenarios where high flexibility and quick changeover, along with relatively low drug quantities to be produced, will dictate the use of SUBs. There are scenarios where blockbusters (original molecules and/or biosimilars) will have to be produced in large quantities in traditional fed-batch, which will justify the investment of 15,000-L SSBs with the associated cleaning validation. There are also scenarios combining the advantages of both SUBs and SSBs, where the seed train will be done in SUBs (maybe in perfusion mode) and enable a faster transition to SSB production bioreactors.

The most important thing to consider for drug manufacturers will be making the right choice at the beginning of their project to prevent any process change that can add significant burden and slow down their move to the next phase.

**BioPharm:** Are there other instances in commercial biomanufacturing processes where stainless-steel materials/equipment would still be necessary because single-use technology would not necessarily be a benefit?

**Bulpin (MilliporeSigma):** Currently, single-use equipment is limited in terms of larger process scale implementation. Dedicated commercial manufacturing in stainless steel still provides large volume capability for large-scale production where single use cannot. Therapeutics with broad indications or large patient populations, such as Alzheimer’s, will continue to leverage stainless steel to process these large volumes. Advantages can be gained with the implementation of a hybrid approach, benefiting from single-use where appropriate. As manufacturers advance therapeutics, they will need to carefully weigh initial speed and flexibility with long-term cost advantages and processing of large volumes.

**Galliher (GE Healthcare):** In the downstream purification process, if more than 10 kgs/batch of drug are being processed, larger stainless-steel piped systems are typically used.

**Paulino (Amgen):** Single-use technology is not as well advanced for purification processes. Some processes require large-scale centrifugation, which may not be as advanced in single use.

**BioPharm:** Can you give an example of a situation where a biological product would require the use of stainless-steel equipment vs. single-use equipment? How is that decision made?

**Galliher (GE Healthcare):** Drugs over 3000 kg/year (such as Humira and Insulin) are produced in stainless-steel bioreactors and purification systems.

**Cole (ABEC):** Single-use microbial fermentation is limited to 1000-L maximum volume at the moment due to heat generation of the microbial
process and the subsequent heat transfer. However, many products require volumes far in excess of 1000 L, so stainless steel is often the only option. Single-use can be an option for the seed fermenters before scaling to larger volumes in stainless steel.

**Bulpin (MilliporeSigma):** At its core, the stainless-steel versus single-use debate has become a balance between capacity and flexibility. If the expected drug substance requirement is enough to justify a facility that is dedicated to one to three products, based on dosage and patient population, then the decision is typically made for a stainless-steel facility. The cost of a stainless-steel facility is largely driven by capital and overhead expenses, which can easily be spread over the large quantity of drug substance produced.

Conversely, a single-use facility that is flexible enough to handle four to six molecules per year is justified if the expected drug substance requirement is constrained by low dosage and/or patient population.

The cost of a single-use facility is largely driven by operating and consumables costs, which have significantly lower overhead and are less sensitive to change-over time.

**Paulino (Amgen):** Companies take different factors into consideration when making the choice between stainless steel and single-use technology. Factors such as compatibility with cell lines, required output, cell line productivity, cost, etc. are just a few that are considered.

**THE FUTURE OF STAINLESS STEEL**

**BioPharm:** As more biomanufacturing facilities move toward single-use, what will be the fate of older/legacy stainless-steel bioreactors and their facilities?

**Paulino (Amgen):** Facilities and equipment will continue to evolve, and lifecycle management will determine how to best repurpose legacy equipment and facilities.

**Cole (ABEC):** We are generally seeing investment in aging facilities since these assets can often be modified cost-effectively to improve productivity, flexibility, reliability, and regulatory compliance. We are actively working with customers to engineer and deliver facility modifications, including introducing single-use elements. With respect to bioreactors, we are modeling and retrofitting systems for new products, higher titers, multi-product capability, and improved sterility, thereby extending their lifecycles.

**Galliher (GE Healthcare):** The typical physical and financial lifetime of stainless-steel facilities has traditionally been 15–20 years. They eventually corrode away and have to be replaced because they are in direct contact with process solutions.

**Bulpin (MilliporeSigma):** Stainless is still alive, and I foresee SSBs will stay around for a while. It is very unlikely that all manufacturing processes using SSBs in fully depreciated facilities will be dismantled in the future. This does not make a lot of sense from a long-term investment perspective, especially for established drugs which will likely be used for some decades. The [return on investment] is the driving force in this case to maintain the existing manufacturing process without new submissions to the regulatory bodies.

The single-use market has largely consolidated around the 2000-L bioreactor and associated downstream systems. This scale balances the risk of film or component failure with the benefits gained from operating highly-productive cell culture batches in a single-use format. While there are some suppliers that provide custom single-use bioreactors at greater than 3000 L, most biomanufacturers have chosen to scale out with multiple 2000-L bioreactors rather than scale up to a larger bioreactor.

Therefore, bioreactor operations that would require higher volumes have to be in stainless-steel. Similarly, in downstream unit operations, manufacturers will continue to leverage existing facilities while incorporating single-use where it can increase efficiency and lower cost or overhead.

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**More on single-use and stainless-steel systems**

For more information on the use of single-use or stainless-steel systems, visit BioPharmInternational.com to read the following:

- Thinking Flexibly in Biomanufacturing
  - www.biopharminternational.com/thinking-flexibly-biomanufacturing
- Buffers Benefit from Single-Use Systems
  - www.biopharminternational.com/buffers-benefit-single-use-systems
- Reinventing the Biomanufacturing Wheel
  - www.biopharminternational.com/reinventing-biomanufacturing-wheel
- Comparing Fed-Batch Cell Culture Performances of Stainless Steel and Disposable Bioreactors
Moving From Compliance to Quality

Too narrow a focus on regulatory compliance may prevent organizations from embracing—and profiting from—quality and operational excellence.

O
ver the past five years, global regulators have started a dialogue with pharmaceutical manufacturers about how best to measure quality (1). Frank discussions are taking place about management and corporate cultures (2) and whether they advance or impede efforts to establish operational excellence and customer-focused quality.

Efforts to study the relationship between quality and manufacturing performance peaked in the 1950s and 1960s. Inspired by thinkers such as Peter Drucker (3), W. Edwards Deming, and Taiichi Ohno, former chairman of the Toyota Motor Corp. in Japan, corporate leaders in a number of industries began to view quality as a revenue-creating opportunity rather than a cost center, and looked for new ways to empower workers to achieve excellence. The work clearly paid off. In 2014, in a study of 60 corporations, the Harvard Business School found that companies with strong quality cultures saved an average of $350 million per year (4).

The first formal operational excellence programs embracing these concepts took off in the pharmaceutical industry in the late 1980s. In 2014, the Parenteral Drug Association (PDA) surveyed pharmaceutical companies on quality practices and set up a task force to help elucidate current connections between culture, behavior, and quality attributes, and to show how quality culture is reflected in manufacturing and quality performance. PDA then teamed up with the University of St. Gallen, Switzerland, to analyze survey results along with data from the Swiss university’s extensive studies of pharmaceutical manufacturing and quality practices. The research focused on such metrics as communication; transparency; commitment and employee engagement; and standardization of requirements. Mature quality practices were defined as being objective and verifiable and included having formal programs in preventive maintenance, risk management, human error prevention, training, and continuous improvement (5). Results of that study enabled the development of a quality culture assessment tool that PDA has used to train 50 firms and more than 100 regulators in the United States and Europe, according to PDA task force leader Cylia Chen Ooi, director of quality at Amgen.

Observers see the need for pharma to expand its definition of quality. “Compliance, rather than a tradition of operational excellence, remains deep in pharma’s DNA,” says Nuala Calnan, founder and principal of Biopharm Excel and a member of Dublin Institute of Technology’s (DIT)
regulatory science team, who worked on the quality culture metrics program with PDA and St. Gallen. “This mindset presents a significant barrier to excellence and must shift if the industry is to move beyond inspection readiness to true patient focus,” she says. The past decade, marked by mergers, downsizing, offshoring, and increased competition, has provided the industry with a number of negative examples of quality culture, for example:

- The quality department of one Big Pharma over-the-counter (OTC) drug subsidiary in the US, whose managers allegedly coerced quality control (QC) lab analysts into passing failed batches. The department was unofficially nicknamed “EZ Pass” (6). Senior managers at the company were ultimately sued for failure to fund adequate QC, resulting in a $22.9-million settlement (7).
- Two Indian pharmaceutical companies, which fired workers after their facilities received warning letters from FDA (8).
- Operators and technicians at a number of Indian and Chinese manufacturing facilities in 2014–2017, who, during FDA site inspections, reacted to auditor requests by shredding documents, pouring samples down the drain, or removing a memory stick from a computer and running away with it (9). FDA has noted document shredding as recently as 2019 in a warning letter citing deficiencies at a facility in India (10).

Observers see the need for more proactive pharmaceutical company managers who actively support and invest in quality efforts and employee training. Toyota’s quality leaders often discussed the need for senior managers to walk the manufacturing, research, and testing laboratory floors (i.e., the gemba, or, in Japanese, the place where truth will be found) to learn directly from employees what the day-to-day problems are, to coach them, and work with them to find solutions. “For gemba to work, managers must talk while they’re out there, not telling but listening, observing, coaching, and enabling employees by removing barriers,” says Calnan.

**WALKING THE TALK**

More pharma companies are encouraging this approach and shifting to peer-review models with leaders being made more accountable and visible. But, as more companies and managers adopt formal gemba walk programs, says Chen Ooi, there is a real need to measure their effectiveness. As she notes, it’s not a straightforward science. “It’s all about behavior and reactions, and you don’t want to blame. You need to build trust with people on the floor so that they feel comfortable raising issues and provide truthful feedback instead of telling you what they believe you want to hear,” she says. Body language and tone of voice are extremely important, she says, and managers need to understand what goes into creating what Harvard professor Amy Edmondson has described as a “safe” environment where people can be honest (11).

It might be beneficial, says Chen Ooi, for executives to have a better understanding of science and engineering concepts in order to communicate more effectively with the people doing the work. But that understanding needs to flow from the bottom up, too. “Leaders in process development, supply chain, and manufacturing also need to be able to translate the very technical aspects of their operations into the more general language of business,” she says.

At the most fundamental level, there is a real need to understand the cost of poor quality in order to weigh potential losses (e.g., of a warning letter or consent decree) against the costs of hiring more quality control staff and investing in more modern analytics or information technology (IT). Georgetown University professor Jeffrey Macher has found that most pharmaceutical companies fail to measure or track the cost of quality within their organizations (12).

To be fair, says Chen Ooi, it can be difficult to quantify the cost of poor quality in dollar values. “It’s really about continuous improvement and preventing issues,” she says. At many pharmaceutical companies today, basic metrics are tracked, such as successful batch release rate, rate of invalid or out-of-specification (OOS) results, and inspection findings. But these are lagging metrics, she says, and only available after something has gone wrong.

Amgen is shifting to a “predict-and-prevent” focus and using artificial intelligence and data visualization to leverage more of the data gathered within the current good manufacturing practice (cGMP) environment that typically remains unused, says Chen Ooi. Using open-source code, available at very low cost, the company has developed a tool for deviation trending inhouse that can be used to uncover systemic problems, she says. The alternative until now was to have people review hundreds of issues, a painstakingly slow process.

**BETTER TRAINING NEEDED**

If the industry is to sharpen its focus on quality metrics and culture, university training should include more industrial engineering-type courses to prepare students to understand and take charge of quality initiatives, says Chen Ooi. “There’s a need to educate students on the concept of quality beyond compliance so that they realize the value and business benefits of quality,” she says.

“In pharma, every mistake or OOS situation requires a full-blown investigation, which requires significant time and resources,” she says.

Forward thinking universities are transforming traditional curricula. “We try to inculcate experiential learning into educational programs,” says Ajaz Hussain, director of the
National Institute for Pharmaceutical Technology and Education (NIPTE), a consortium of 17 universities that include Rutgers, Purdue, Duquesne, and the University of Puerto Rico. NIPTE members have been moving toward integrated multidisciplinary courses that emphasize problem solving and critical thinking and include real-world problems, says Hussain, while also including certification to track continuous learning and improvement.

**SHAME, BLAME, RETRAIN?**

Corporate training programs can also be an obstacle to building a quality culture. “In organizations with a lower level of quality culture maturity, we often see the ‘shame, blame, and retrain’ approach being used. This is no longer acceptable to regulators,” says Calnan.

“The onus is on companies to create good onboarding and training processes to address the gap between university training and required on-the-job knowledge,” Calnan says. “But many organizations still use traditional onboarding, where success is often based on how many people signed up to train on whatever the topic is, rather than how well they mastered the material,” she says. Instead, she says, companies need to look at how tacit knowledge can be transferred between teams and coaches and mentors.

Technologies such as augmented and virtual reality can be useful because they allow the subject matter expert and the trainee to confer directly. Calnan notes a course that one company uses to train employees on column packing for chromatographic skids. “This is a very specific activity that can cause major problems if done wrong, but, for orphan drugs, operators may only be making two batches a year. Virtual reality refreshes their knowledge and lets them walk through the procedure the day before,” she says.

Hussain sees professional development as crucial to corporate training programs. “Deming emphasized appreciation for systems and the psychology of change. That’s where emotional intelligence comes in and where we use the term ‘culture of quality,’” he says. “You need a critical mass of leaders who are self-authored and self-transforming in order to achieve what Harvard education professor Robert Kegan called ‘orders of consciousness’” (13), he says. Those leaders must bring the rest of the staff up to support continuing education and continuous professional development.

Quality will ultimately depend on understanding the customer. When she visits companies, Calnan says, operators and technicians usually can’t tell her who the patient is that they are manufacturing products for. But even companies that cannot afford “patient engagement days” can bring the patient into their manufacturing and quality efforts, says Calnan.

“Why not have a lunch-and-learn session on corrective and preventive action (CAPA)? Take the last three complaints, get the team together and talk about them and how they might have been avoided,” she advises.

More advanced technology such as PAT, modeling, and AI can play a significant role in improving quality. However, many smaller companies often complain that they cannot invest in new technologies. Chen Ooi disagrees, because the potential savings and benefits of using the tools can far surpass the cost of investment. “People need to think about creative ways of stimulating the use of new tools (e.g., by creating small pilot projects to demonstrate the benefit of a specific technology). With artificial intelligence, for instance, a lot of the coding needed to build solutions is open source and doesn’t cost a lot,” she says.

Overall, training will be crucial to building a culture of quality. “People come to work wanting to do the right thing. It is all how managers send the message down and how they create an environment of trust. That is really the bottom line,” she says.

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Accepting the Challenge of Protein Characterization

Protein characterization is a critical part of drug development, but as there are still limitations with available techniques, industry needs to look at technological advances to meet the specific requirements of complex molecule characterization.

FELICITY THOMAS

Protein therapeutics are a promising class of drugs that are increasingly coming to the fore in development pipelines as a result of their utility in difficult-to-treat diseases. Yet, these complex, large-molecule drugs pose significant challenges for developers and regulatory bodies alike.

An important issue for protein-based drug developers is that of structural characterization, which can help in understanding whether or not a drug product will be stable and of sufficient quality to be launched at all. “It is critically important that the complete and in-depth characterization of therapeutic proteins is performed throughout all stages of the drug discovery and development process,” says Simon Cubbon, senior global marketing manager, chromatography and mass spectrometry, Thermo Fisher Scientific. “Ultimately, this facilitates the transfer of appropriate knowledge throughout the pipeline, ensuring product consistency, safety, and efficacy.”

In agreement, Jeff Zonderman, chief commercial officer of RedShiftBio, highlights the concerns around how stress conditions, manufacturing processes, and storage may affect protein structure and adds that drug developers are limited by current analytical tools that do not offer sufficient insight. “This is especially the case with stability and aggregation, where earlier detection and monitoring in the development and manufacturing processes result in better, more effective drugs,” he notes. “Promising biological drug candidates, those that exhibit therapeutic activity and inherent stability, as assessed via simple screening techniques, become subject to increasing levels of structural elucidation as they progress through the pharmaceutical pipeline.”
CHARACTERIZATION AT EVERY STAGE

Protein characterization, along with demonstrating a product’s consistency and reproducibility, are imperative for developers aiming for a quality product, states Brian R. Berquist, director of process development and technology transfer at iBio. “Obtaining information on your protein early on is a way to examine the quality and consistency throughout the drug development cycle,” he asserts. “Protein characterization is critical even in the earliest stages of process and drug development. The process development phase is when one can get a first glimpse at the potential product molecule and how the purification processes applied affect it.”

During early development stages, it is possible to make changes easily to address any potential purity issues. “In some instances, the product may be susceptible to proteolytic activity, either during expression or during purification, so being able to identify small changes in product mass and the amino acid location of that proteolytic activity allow one to address the issue in a logical manner early on instead of having a process where each step must be re-examined due to changes made,” Berquist says. “Additionally, as purification steps are developed, one is selecting based upon properties of the protein molecule itself. Sometimes a purification step or steps can enrich a certain proteoform, multimer, or glycoform that is not highly desirable. Again, it is easier early on to obtain this knowledge and change the purification accordingly.”

Going beyond the early stages of development, and as processes start to become more fixed in nature, Berquist explains that protein characterization can be used to examine the vigor of the purification process on the whole, as well as for each unit operation. “Protein characterization provides critical information regarding the reproducibility and robustness of each step in the process and the purification in its entirety,” he says. “When the process is locked, and manufacturing begins, it is essential to characterize each lot produced to ensure that a quality product is being generated routinely and consistently.”

During early development stages, it is possible to make changes easily to address any potential purity issues.

A CHALLENGING ENVIRONMENT

“In today’s challenging pharmaceutical environment, research scientists are pushed to screen drug candidates as quickly as possible to increase chances of reaching clinical trials,” says Bill Barrett, product specialist at W.L. Gore’s PharmBIO Products business. “Using monoclonal antibodies as an example, speeding the purification process leads to more candidates and higher productivity.”

Adding to the requirements of reduced time and cost, and improved research productivity, Scott Peterman, senior global marketing manager, chromatography and mass spectrometry, Thermo Fisher Scientific, emphasizes that scientists are also now developing advanced protein drugs that are more extensively engineered and, as such, more complex. “As complexity increases, there are opportunities for greater levels of post-translational modifications and molecular heterogeneity,” he says. “Understanding the complexity of a protein-based therapeutic, and being able to control these modifications and variations, is becoming increasingly more difficult but remains critically important.”

Therefore, bio/pharma scientists are required to employ a cornucopia of various analytical technologies and strategies to adequately characterize protein-based therapeutics, continues Peterman. “Each analytical technology or strategy presents its own knowledge requirements and challenges, which scientists and vendors alike must address,” he notes.

Looking at analytical techniques in particular, Richard Moseley, chief technologist at Microsaic Systems, highlights that most can be categorized into two facets—either on-line with low specificity or off-line with high specificity—potentially challenging the ability to obtain answers fast. “In addition, the protein products are in complex chemical cell media making exact identification difficult. Therefore, some critical quality attributes are difficult to characterize and require complex workflows,” he says.

Furthermore, Moseley stresses that established analytical techniques suited to small-molecule drugs have been found to be unsuitable for bioprocessing. “So, biopharma scientists need to look to new techniques, specifically developed for their challenges and workflows to meet the complex needs of bioprocessing,” he asserts.

For Zonderman, challenges lie in the structure of drug studies, irrespective of dosage requirements. “Defining an optimal formulation and manufacturing route relies on assessing the impact of variables such as processing conditions including temperature and applied shear stress, and storage,” he says. “Stress-induced structural changes may have significant consequences including a loss of efficacy, and in the worst case present a safety risk, so demonstrating comparability (that successive stages of formulation, manufacture, and storage do not materially impact the structure of the drug)
and stability up to the point of administration is essential.”

**PROTEIN AGGREGATION: AN UNDESIRABLE PROCESS**

Aggregation—where proteins bind together and form undesirable impurities—can be detrimental to protein-based therapeutic development. These clusters of molecules can result in an incorrect drug dosage, or unwanted and even fatal immune responses to the drug, stresses Peterman.

“Consequently, monitoring protein aggregates is important for safety and quality assurance,” he adds. “Complete characterization and in-depth structural insights allow scientists to better understand what factors can lead to aggregation and undesirable outcomes, aiding clone selection and the delivery of a robust biotherapeutic that will not aggregate undesirably.”

This common indicator of protein instability, aggregation, can occur both upstream and downstream and can result in a product being deemed unfit for launch, continues Zonderman. “Characterization can help by giving insight into the onset of aggregation under certain conditions and help developers better formulate drugs to minimize aggregation or eliminate bad drug candidates earlier in the process,” he notes. “Being able to predict aggregation and resolve when you have true aggregation or self-association is critical.”

“Protein aggregation typically has been observed to be detrimental for both product activity and stability, as well as leading to the formation of higher levels of anti-product neutralizing antibodies in-vivo,” summarizes Berquist. “By applying rigorous size-exclusion chromatography (SEC) methodologies, we monitor even low levels of protein aggregation and use these data to optimize drug formulation to prevent aggregate formation.”

**THE RISE, AND DIFFICULTIES, OF BIOSIMILARS**

It is well-known that many branded protein-based biopharmaceutical products are facing patent expiration in the coming years, and so, the growth of the biosimilars market is an inevitability. As specified by regulatory bodies around the world, in some form or another, biosimilar products must be proven to be highly similar to its reference product with no clinically meaningful differences in terms of safety, purity, and potency. The primary goal of protein characterization for biosimilars is to provide sufficient evidence of similarity to the originator product, adds Berquist. “However, the problems with this are multifaceted,” he continues. “First, there are difficulties in obtaining sufficient supplies of the innovative drug product for comparison. Second, there is technological gap between original drug product characterization results and the instrumentation available for characterization of the biosimilar. The challenge is to prove that any observed differences not significant and do not have clinical relevance.”

Concurring with Berquist, Cubbon further explains that biopharmaceutical companies exhaustively characterize therapeutics and associated manufacturing processes to improve the specificity of the patents, and these specifics may not be accessible to the biosimilar developers. “Consequently, the biosimilar developers are required to perform characterization to the same exhaustive levels,” he continues, “for example, to determine protein drug glycosylation, aggregation, and charge variant profile.”

As a result of this level of specificity that may be required when approaching biosimilar development, costs may not be reduced as significantly as is possible when approaching a small-molecule generic drug, for example. “The use of biosimilars, with such closely comparable performance to an original drug that can be used interchangeably, can provide sufficient evidence of similarity to the originator product, adds Berquist. However, the problems with this are multifaceted,” he continues. “First, there are difficulties in obtaining sufficient supplies of the innovative drug product for comparison. Second, there is technological gap between original drug product characterization results and the instrumentation available for characterization of the biosimilar. The challenge is to prove that any observed differences not significant and do not have clinical relevance.”

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As a result of this level of specificity that may be required when approaching biosimilar development, costs may not be reduced as significantly as is possible when approaching a small-molecule generic drug, for example. “The use of biosimilars, with such closely comparable performance to an original drug that can be used interchangeably, has the potential to drive down healthcare costs but is highly dependent on the rigorous demonstration of similarity in a wide range of attributes including protein content, activity, and stability,” asserts Zonderman.

**TECHNICALLY LIMITED**

Currently, there are many methods available that look at different attributes of the protein molecule, however, these methods are not without
limitations. “Many of the techniques and tools available are inherited from pharmaceutical’s roots in small-molecule drugs, which are normally unsuited to the complex bioprocessing workflows and cell media used,” says Moseley.

Traditional assays, such as capillary electrophoresis (CE) or liquid chromatography coupled with ultraviolet (LC-UV), are robust and reliable techniques; however, they can only provide limited information on the critical quality attributes (CQAs) that need to be measured, stresses Cubbon. “This means that numerous assays are required to confidently cover these CQAs and ensure the correct information is obtained,” he adds.

According to Zonderman, there is a dependency on what technology is used and how it is applied, but in general, key limitations of current techniques include dynamic range, sensitivity, and automation (both analysis and data processing). “Many of the currently available technologies may meet some of the needs for research, but are a challenge for biopharma to move into more downstream, QA/QC [quality assurance/quality control], and process monitoring applications,” he notes.

CRITICALITY OF CHARACTERIZATION

The detailed definition of the structure of a drug molecule can provide a basis for scientists to identify structure-function relationships that enable an understanding of how a drug is efficacious, explains Zonderman, but beyond this the structural characterization of proteins plays a critical role through the drug development lifecycle. “In particular, investigating structural changes is the key to understanding and controlling the factors and mechanisms associated with stability and aggregation,” he says.

“Characterizing proteins during drug development is essential in reducing drug development times and manufacturing costs, and is critical for safety reasons,” agrees Moseley.

“Furthermore, through protein characterization, industry is now capable of creating personalized medicine for patients.”

Yet, challenges and limitations remain in the ability to characterize these complex molecules sufficiently, and industry needs to be fully capable of managing the complexity of the information that is obtained through characterization, says Berquist. “As technology advances, industry will gain an ability to address increasingly intricate questions about protein products,” he summarizes. “Today, we have the capabilities to analyze intact macromolecules to the detail of detecting microheterogeneities leading to difficulties associated with data interpretation and refinement.”

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**Call for Peer-Review Papers**

*BioPharm International* accepts four types of peer-review papers that are considered: standard data-driven, novel research; topical literature or patent review; technical case studies/technical application notes; and science-based opinion papers.

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Submitted papers are initially screened by the editors, then submitted for formal review by a member of the editorial advisory board, who will review the article for technical interest and content in a double-blind review process. Article acceptance is conditioned on the reviewer’s approval. Once accepted for publication, a paper typically is published within three to five months.

Peer-review papers are published in the print and digital editions of *BioPharm International*, and on www.BioPharmInternational.com. Links to the online versions of peer-review papers also are featured in e-newsletters distributed to the publication’s audience.

To learn more about the peer-review submission process, click the Submission Guidelines link on www.BioPharmInternational.com.
Manufacturing for clinical trials requires addressing complex packaging, labeling, and logistics issues. New patient-centered trial models and the growth of personalized gene and cell therapies have added additional degrees of difficulty to the process. Creative management and use of interactive response technologies (IRTs) solutions (Sidebar) are helping sponsors and contract partners improve overall efficiency and reduce waste. In this article, Matt Blume, general manager of global business operations for Catalent Pharma Solutions, shares insights and best practices.

**PREVENTING THE CMC DISCONNECT**

**BioPharm:** How do you address the disconnect between chemistry, manufacturing, and control (CMC) and manufacturing specialists in your work with clients?

**Blume (Catalent):** We include clinical project managers in early phase manufacturing discussions with the sponsor. For example, in our San Diego facility, we have co-located clinical project managers in the CMC plant so that they can be included in the earliest possible project discussions. Even though these discussions may not focus on clinical supply, the earliest stage of the product is the perfect time to highlight areas that sponsors should consider (e.g., general project timelines and packaging configuration options).

Early development batch production is a good time to place product down on stability in multiple material configurations. Doing this very early in the process allows meaningful data to be gathered as soon as possible, ensuring that the most patient-friendly package is designed, and allowing for potential savings in Phases II and III if data can be established that allow for higher shipping temperatures. There is no downside to ensuring that all team members are engaged throughout the process. The interaction of the different specialties not only helps the specific project being discussed, it also builds cross-functional knowledge, strengthening the CMC team’s understanding of clinical concerns and the clinical team members’ knowledge of CMC challenges.

**LABELING BIOLOGICS**

**BioPharm:** What are the most challenging packaging and logistics issues involved in clinical trial manufacturing, and how (and when) should they be addressed?
Blume (Catalent): One challenging task is the labeling of biologics and gene therapy products prior to freezing. At the point of fill/finish, minimum label content must be determined so that it can be used for many different countries and destinations. This needs to be addressed very early on. Co-locating clinical supply team members to focus on label design and clinical challenges within the manufacturing team is extremely helpful, especially since these teams have little clinical trial experience, unlike their peers at traditional solid dosage form manufacturing plants.

With smaller vials and syringes that will be subjected to cold temperatures, it is very important to ensure that the adhesive used for the label is appropriate and that as much of the label text as possible will fit within a small area. For example, many gene therapy treatments are packaged in 3-mL vials, minimizing the real estate available for vial labels. Early involvement with clinical specialists is key to thinking through minimum label requirements and design.

Another challenge is the blinding of increasingly complicated therapies including biologics and pre-filled syringes. Producing a matching placebo is no longer simply a matter of making a matching tablet or capsule. Many factors must be considered when blinding an injectable or intravenous therapy. With injectable products, the solution's appearance must be verified before administration, so the matching placebo must match all of the characteristics of the active product.

NEW TRIAL MODELS

BioPharm: Where do you see direct-to-patient models having the greatest impact on manufacturing and logistics?

Blume (Catalent): By delivering directly to the patient from a clinical packaging site, the manufacturing

Continues on page 46
The quality control (QC) microbiology laboratory plays an essential role in pharmaceutical manufacturing and product release. It is responsible for multiple tasks, including:

- Environmental monitoring (sampling, bioburden counts, microbial identifications, and tracking and trending of data)
- Investigating out of specifications, deviations, and contamination events
- Implementing and validating QC methods and testing based on release specifications.

These activities must follow the company’s quality procedures and federal regulations. Because these establish the state of control of the manufacturing environment and are critical for product release, it is imperative that the QC microbiology laboratory perform tests accurately, reliably, and timely.

If product release is delayed, there is additional cost in holding inventory, disruption in the manufacturing schedule, and possible drug shortage and regulatory scrutiny. Even worse, if a contaminated or ineffective product is released, patient health is impacted, and lives are at risk. The manufacturer also suffers regulatory consequences and recalls, a financial loss, and damage to the company reputation.

To meet the necessary high standard of quality in an efficient manner, certain laboratory best practices should be followed regarding training, standard operating procedures (SOPs), data integrity, appropriate rapid methods and technologies, and a commitment to Lean; Sort, Set in order, Shine, Standardize, and Sustain (5S); and Six Sigma concepts. These best practices ensure each technician is operating to the same standard and performing tasks consistently and allow the QC laboratory to increase accuracy and efficiency.

Jessica Rayser is product manager, Accugenix, Microbial Solutions, at Charles River.
Developing a Robust CQA Monitoring Method via Multi-Attribute Monitoring Principles for Therapeutic Monoclonal Antibody Development, Manufacturing, and Lifecycle Management

ON-DEMAND WEBCAST  Aired September 10, 2019

Register for this free webcast at www.biopharminternational.com/bp_p/bioaccord

Quality-by-design (QbD) principles outlined by FDA require a deep understanding of the biopharmaceutical product and process to ensure the desired product quality is met at the end of the development cycle. Aiming to support QbD and to gain greater understanding of complex biotherapeutics, there is a trend to move mass spectrometry (MS) into labs that are more familiar with optical methods. This has facilitated the introduction of liquid chromatography (LC)-MS-based multi-attribute monitoring (MAM) methods for the robust monitoring of critical quality attributes (CQAs) at the molecular level.

In this webinar, learn about the development of a fast and robust CQA monitoring method based on multi-attribute monitoring principles using a compact, compliance-ready LC-MS system. The presentation will demonstrate how the method can be easily transferred from development to manufacturing through commercial product lifecycle management.

In this webinar, you will learn about:

- Establish a high throughput, low artifact, subunit mass-based multi-attribute monitoring workflow
- Identification and monitoring product quality attributes such as N- and C-terminal heterogeneity, oxidation, glycation, aglycosylation, afucosylation, etc.
- The purposeful design and embedded technologies to overcome the anticipated deployment challenges into the manufacturing environment

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ON-DEMAND WEBCAST
Aired July 17, 2019

For questions contact Kristen Moore at KMoore@mmhgroup.com
BARE NECESSITIES: TRAINING AND SOPs

SOPs are a critical component of manufacturing. There have to be written instructions on how to perform each task—not just on the production floor but in the laboratory as well. US 21 Code of Federal Regulations 211.100 states (1):

“(a) There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Such procedures shall include all requirements in this subpart. These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit.

“(b) Written production and process control procedures shall be followed in the execution of the various production and process control functions and shall be documented at the time of performance. Any deviation from the written procedures shall be recorded and justified.”

While it can be easy to dismiss the task of writing SOPs as a paperwork exercise, it is important to understand their value. SOPs ensure that every technician is operating the same way, which yields more consistent test results. Procedure training documents should be extremely detailed; it can be dangerous to assume that technicians understand what is implied or what seems like common sense. To that aim, it is important to review procedures regularly to be sure they are up to date; technicians in particular should be sure to review SOPs for accuracy. Pictures, easy schematics, and flowcharts—anything that makes it easier for the lab tech to read, understand, and follow a SOP—should be included in such a document.

Technicians should be trained on each SOP as determined by the laboratory manager and quality assurance department. Typically, each job role has a defined training matrix with all the SOPs listed that relate to those job functions. However, all personnel should also be trained on quality procedures, good manufacturing practices (GMPs), and documentation. Training matrices should be reviewed periodically as job functions evolve over time with additional responsibilities and headcount. Documentation of training is also important as those records are often requested by auditors.

Training should obviously encompass more than just reading the SOP. Particularly for complicated tasks, training should include a period of observation, then practice while under observation, and finally a proficiency test. The laboratory should have defined trainers who are experienced technicians in charge of training. When SOPs are revised, the technicians should be trained on the new version, and skills should also be assessed on a periodic basis.

It is no small investment to teach a new technician how to perform tasks according to the company SOPs. Therefore, to maximize efficiency, training should be strategic so the new technician can contribute to some tasks while still learning others. The laboratory can then manage their workload more effectively.

DATA INTEGRITY: NOT JUST A CATCH PHRASE

Data integrity remains a hot topic in the pharmaceutical industry, and regulators are auditing for compliance in this area. While the enforcement may be new, the regulations in 21 CFR 211.180 have been in place for almost 25 years. The focus is not just in the United States, but globally as well. Rx 360, an international pharmaceutical supply chain consortium, provides a comprehensive list (2) of data integrity resources. Data integrity is defined as “the maintenance of, and the assurance of the accuracy and consistency of, data over its entire lifecycle, and is a critical aspect to the design, implementation, and usage of any system which stores, processes, or retrieves data” (3).

It is expected that companies comply with the ALCOA+ (attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring, available) principles of data integrity in Table I. This applies to not only paper-based systems, but computer systems and software as well. For the laboratory, adhering to data integrity principles is critical as their tests are responsible for releasing product to the public. Modification or loss of data could pose a risk to patients.

Any reduction of human error in the laboratory will bolster the company’s data integrity and, consequently, the company’s regulatory position. To this end, many labs are moving to automated equipment and laboratory information management system (LIMS), provided that they are validated and follow ALCOA+, as it minimizes handwritten records and inconsistencies. Streamlined workflows and less handling can significantly speed up testing while providing more reliable data. Examples of this are Charles River’s cartridge technology and robotic system for endotoxin testing. The data output for these are readable, contemporaneous with data and time stamps, attributable with operator logins, original, accurate, and consistent. The data files can be saved electronically to remain enduring, available, and complete.

A particular challenge in the QC laboratory is the difficulty of compliance with maintaining original (or raw) data. For example, the agar plate for bioburden testing cannot be saved so it becomes even more important to have an accurate colony count because that count will become the enduring data. In these cases, many companies are moving to the “four-eye” method where a second technician reviews and signs off on the result. However, this could be considered a subjective test, along with Gram staining. It is possible that two
How are these different results rectified if the workflow is being followed. This prevents errors from occurring, documents principles of data integrity.

Table I. ALCOA+ (attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring, available) principles of data integrity.

<table>
<thead>
<tr>
<th>ALCOA+ Attribute</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attributable</td>
<td>Data must be attributable to the individual or the system producing the data to associate data production to a responsible party and to track any changes occurring to the data.</td>
</tr>
<tr>
<td>Legible</td>
<td>Data must be everlasting and must be stored in a fashion that safeguards readability and accessibility for all the timeslots in which the data might need to be accessed or legally referenced.</td>
</tr>
<tr>
<td>Contemporaneous</td>
<td>Data are to be recorded in the moment in which data are generated, an event is observed, or a failure is detected.</td>
</tr>
<tr>
<td>Original</td>
<td>Data must be used or presented as it was created, or in case they have been modified, changes must be traced so that is possible to date back to the original form.</td>
</tr>
<tr>
<td>Accurate</td>
<td>Data must be routinely verified through repeatable calculation or analysis to ensure no error is in place.</td>
</tr>
<tr>
<td>Complete</td>
<td>All data must be in place and have full-length features, thus reporting any repetition or reprocessing executed.</td>
</tr>
<tr>
<td>Consistent</td>
<td>All of the flow of an analysis must be coherent and performed in the expected sequence in a temporal manner.</td>
</tr>
<tr>
<td>Enduring</td>
<td>Data must not be written and registered on any physical objects besides notebooks or electronic media in the systems.</td>
</tr>
<tr>
<td>Available</td>
<td>Data must be accessible for review and inspections over the lifetime of the record.</td>
</tr>
</tbody>
</table>

people view color differently or may count one colony as two (or vice versa). How are these different results rectified and justified? Subjective tests should be avoided whenever possible to reduce the workload redundancy and possible discrepancies.

All QC micro labs would benefit from using an efficient LIMS to expedite processes and ensure data integrity compliance. As an example, the Charles River Accugenix microbial identification laboratories have a custom LIMS that manages technician training, equipment, reagents, samples, and testing workflows. Each processing step is documented by scanning a series of barcodes. There is instant feedback to confirm that the technician is trained in that operation, the reagents are within expiry and released by QA, the equipment has been calibrated and appropriate for that step, and that the workflow is being followed. This prevents errors from occurring, documents batch records, and gives the lab the visibility to work efficiently.

Also, in connection to the last section on training, FDA clearly stated in their Data Integrity and Compliance with Drug CGMP Questions and Answers Guidance for Industry that all employees should be trained on data integrity (4). Question 16 of that document says “Training personnel to prevent and detect data integrity issues is consistent with the personnel requirements under CFR 211.25 and 212.10, which state that personnel must have the education, training, and experience, or any combination thereof, to perform their assigned duties.”

RAPID METHODS AND TECHNOLOGIES: MODERNIZING THE LAB

Rapid or alternative microbiological methods may provide significant benefits to the pharmaceutical laboratory. It is best practice for the laboratory manager to stay informed of available technologies and to implement them when appropriate. As regulators propose revisions to existing industry guidelines, they specifically call for modern methods to be implemented. Modern methods are defined in the Parenteral Drug Association’s (PDA’s) Technical Report 33 (5) as:

“A novel, modern, and/or fast microbiological testing method that is different from a classical or traditional growth-based method, such as agar plate counting or recovery in liquid broth media.

“The alternative or rapid method may utilize instrumentation and software to manage the testing and resulting data, and may provide quantitative, qualitative, and/or microbial identification test results.

“Automated technologies that utilize classical growth-based methods may also be designated as being novel, modern, or rapid, based on their scientific principle and approach to microbial detection.”

European Pharmacopoeia (Ph. Eur.) 5.1.6 states: “Alternative methods may be used for in-process samples of pharmaceutical products, for environmental monitoring, and for industrial utilities (e.g., production of water, steam, etc.), thereby contributing to the quality control of those products” (6).

Introducing new technologies may seem daunting, but it needs to be done for long-term advantages as well as progressing the industry’s standards for product quality control. Possible benefits include reduction in costs, faster time to results, less labor, and increased data integrity. To recognize these benefits, however, it is imperative that the rapid methods and technologies are thoroughly vetted and validated. During the evaluation, include the following points of consideration:
• What critical information does the method/instrument provide? Does it provide equivalent or more information than the current test?
• Can the method/instrument be used across many of your products or is it compatible with only a small number?
• Can the method/instrument process all your samples without an extra investment of space, people, and additional instrumentation?
• Can you validate it?

Many people are intimidated by the perceived challenges of implementing rapid methods. However, there are many available resources, such as PDA’s TR 33, United States Pharmacopeia (USP) <1232>, Ph. Eur: Informational Chapter 5.1.6, and USP draft <1071>. The vendor should also be able to offer the appropriate regulatory, validation, scientific, and technical support. For example, Charles River’s Celsis instrument for microbial limits and sterility can assist by providing a validation protocol. While there is extra work upfront to validate the method, the payoffs should justify the effort. While some rapid methods and technologies can provide significant value and savings quickly, the wrong system can cause frustration, delay, and waste. Understanding the key criteria in selecting a rapid method will facilitate choosing a system that will best provide rapid, relevant results while minimizing testing risk and optimizing resource allocation.

TOOLS FOR IMPROVEMENT: LEAN/5S/SIX SIGMA CONCEPTS

The final best practice to note for the QC laboratory is a commitment to Lean manufacturing, 5S, and Six Sigma concepts. Lean and 5S principles are designed for maximizing efficiency by minimizing waste and Six Sigma is focused on continuous improvement. They are harmonized philosophies in the sense that Lean and 5S can identify areas of improvement and Six Sigma can facilitate the process. Since the lab is busy with many activities, implementing some of these concepts can save time and money.

First, the laboratory can identify areas of improvement based on Six Sigma’s eight areas of waste, sometimes referred to by the acronym “DOWNTIME.” These eight areas include: defects, overproduction, waiting, non-utilized talent, transportation, inventory, motion, and extra processing. For example, defects in the lab could be downed instruments or raw materials that do not pass incoming inspection. Any failed or invalid test would also be considered a defect. Then the Six Sigma principles of DMAIC (define, measure, analyze, improve, control) could be applied. Lean principles defined the problem, and in the example of an out of service instrument, the “measure” (or metric for tracking) may be the number of times the instrument goes down in six months or how long it takes to make it functional again. “Analyze” is the period of collecting data and reviewing the metric for trends or conclusions. “Improve” consists of designing and implementing a solution, which could be additional preventative maintenance of the instrument. Finally, “control” the problem by ensuring the implemented solution truly solved the problem and no other problems appear. The idea is that this is not a static, one-time event, but a dynamic and ongoing process.

5S can also help reduce waste in the laboratory. The concept encourages simplification by keeping only what you need and organizing materials. This can save time by making it easier to find the necessary supplies and prevent mistakes by eliminating unnecessary options. For instance, keeping multiple sets of each reagent makes it more difficult to find the particular one you need and increases the probability that a wrong or expired reagent could be used. By sorting through and discarding expired reagents, and organizing what’s left, human error is minimized.

CONCLUSION

The best practices discussed in this article for the pharmaceutical and biotechnology laboratory integrate well with each other. A robust training program includes GMP documentation and thus data integrity principles. Implementing a rapid method may reduce time (and waste) and labor (simplified training) while supporting data integrity. Continuous improvement of lab operations facilitates training and reduces inefficiencies so the value it brings can be recognized in both the long and short term.

Given all the laboratory’s responsibilities and its role in releasing product, implementing these best practices will enable the microbiology laboratory to operate accurately, reliably, and timely. Strong personnel training, detailed SOPs, commitment to data integrity, investigation and implementation of appropriate modern methods, and employing Lean and Six Sigma methodology initiatives support the entire company’s pledge to manufacture safe and effective products.

REFERENCES

Covering the business and science of biopharmaceutical development and manufacturing worldwide

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De-risking Biologics Development Through Advanced Mass Spectroscopy Approaches

Using advanced HDX-MS and native MS techniques can improve the identification of potentially successful biologic drugs and de-risk CMC and clinical designs.

JENNIFER S. CHADWICK

The overall success of moving drugs from Phase I clinical trials to approval is approximately 10% (1), indicating an enormous opportunity to improve approaches to the development of biologic drugs and more effectively achieve intended clinical outcomes. Advanced analytical assessment of molecular attributes has been demonstrated to enhance the likelihood of success of biologic drugs in clinical development, which has become more important as an increasing proportion of the therapeutics pipeline is made up of biologic drugs. This article discusses how the use of hybrid mass spectrometry (MS) approaches can inform and de-risk decisions to help enable success of biologic development programs (2).

Biologics are large, complex molecules produced in living cells. Therapeutics on the market and in development include monoclonal antibodies (mAbs) and related analogs, recombinant human proteins, enzyme-replacement therapies, fusion proteins, antibody-drug conjugates, bispecific drugs, and a wide array of gene and cell therapy approaches.

The biologic therapeutics class also represents an economically important sector. The total global biologics market was worth $255 billion in 2017 (3) and is projected to grow to between $400 billion and $581 billion by 2025/2026 (3,4). North America alone is predicted to have a revenue share of the market of more than 40% by the end of 2024 (5). The biopharmaceutical industry’s investment is growing. In 1980, US members of Pharmaceutical Research and Manufacturers of America (PhRMA) spent $2 billion on biopharma R&D. By 2015,
this amount had risen to an estimated $58.8 billion (5).

Biologic drugs offer unprecedented innovation, rapid growth, and major opportunities, both for biopharma companies and for patients, but their successful development can be challenging. Even with the greater knowledge and process improvements put in place since the 1980s, more than 90% of all drug candidates fail between Phase I and approval (1), and over half will fail in Phase III (6). According to an FDA report, there were more than 6300 biopharmaceuticals in clinical development globally in August 2016 (7). This has increased from 5400 products in December 2011. Of the products in clinical trials, 2660 were in Phase II and only 932 in Phase III, confirming the high rate of attrition (7).

Biologics are costly to manufacture at clinical and commercial scale, and the smallest changes in manufacturing processes can have an impact on drug safety and efficacy. Approaches that inform on critical quality attributes, critical process parameters, and correlations with clinical outcomes can reduce the failure rate and could help to speed drugs through development and ultimately reduce the enormous aggregate costs of drug development.

**BETTER KNOWLEDGE MAKES FOR BETTER DRUG DEVELOPMENT**

Understanding a candidate drug and how it interacts with the target across a number of clinically relevant doses improves the chances of a successful transition from preclinical to clinical development. Acquiring as much information as possible at an early stage will help researchers to select the best candidate and corresponding dose, inform the chemistry, manufacturing, and controls (CMC) program, and design better clinical trials. Key steps include defining the binding site profile and target site engagement as well as further understanding the drug’s mechanism of action (MoA).

How the candidate drug interacts and engages with its target play a major role in its efficacy and are important markers of success. By creating an accurate profile and gaining a better understanding of the interaction between drug and target, researchers can select the best candidates and further optimize their safety and efficacy. By using the right analytical approaches, researchers can generate insights into drug candidates’ molecular and chemical attributes and further develop correlations between these attributes and biological function and/or clinical outcomes, which will further improve candidate selection and optimization.

**GAINING A BETTER UNDERSTANDING**

Analytical technology is progressing fast, providing researchers with more and better tools to understand biologic drug-target interactions and mechanism of action. There is a wide variety of high-throughput low-resolution methods used to detect the binding between molecules and establish the binding affinities, including the following:

- Surface plasmon resonance (SPR)
- Biolayer interferometry (BLI)
- Analytical ultracentrifugation (AUC)
- Light scattering techniques
- Isothermal titration calorimetry (ITC)
- Size-exclusion chromatography (SEC).

These techniques all allow rapid data collection; however, interpreting the results and applying them to strategic decisions about drug candidate selection can be challenging, if not confounding in many cases. All of these approaches require the analysts to make assumptions while interpreting the data, which can result in variations in the results. For example, calculating the size of biologics using AUC and SEC requires an assumption of the shape of the molecule. If this assumption is incorrect, the size and therefore the stoichiometry may be incorrect. Complexes, which include a number of different components, can further affect the data analysis.

Detailed molecular characterization methods using high-resolution structure tools give researchers access to much greater detail about the interaction between biologic drug candidates and their target sites, right down to the level of the residues and regions directly involved in binding or affected by the binding process. These also provide a better understanding of the impact of components within complexes, and how these can affect the mechanism of action, and the eventual outcomes in vivo and in clinical trials. This level of characterization is further important in CMC to make better predictions of the stability of the biologic molecules as they move from drug discovery to drug development, allowing researchers to make go/no-go decisions or continue the optimization process. Detailed characterization also allows assessment of the quality of in-process materials at every step. At the clinical stage, high-resolution techniques are important to support the scale-up/out process and to ensure that the drug product meets the same specifications when it is produced in larger batches and/or reproduced in different facilities.

The disadvantage of high-resolution methods is that they take longer and require greater resources than low-resolution techniques.

**THE BENEFITS AND APPLICATIONS OF MS**

MS can be used to assess a wide range of biologic species, across a breadth...
The two key MS approaches for characterizing binding and MoA are hydrogen deuterium exchange (HDX) MS and native MS (see Table II).

HDX-MS measures the rate of exchange of protons between labile amides and aqueous solution. This analysis approach can map binding site interactions, including epitopes on antigens, paratopes on antibodies, protein-protein/ligand interfaces, and self-association as well as identify conformational changes induced by binding.

Native MS is a gentler technique that determines the size of intact macromolecules, proteins, and complexes while still in their folded state as well as aggregated species. The technique has been used successfully to analyze multi-protein assemblies, viral capsids, and mAb-antigen and protein-small molecule complexes. Data from native MS analysis can confirm the stoichiometry of subunits in heterogeneous complexes, and further MS analyses can help to verify the individual components in detected complexes. An example of this is the determination of the relative levels of correctly paired heteromeric bispecific chains and incorrectly paired homomeric species in the production of a bispecific antibody candidate. An important example application is determination of the level of homotypic anti-CD3 pairings in a bispecific product for assessing potential risk of immune reactions caused by CD3 cross-linking.

HDX- and native MS can both play an important role in strategy and decision-making in drug development and CMC. By mapping interactions between antibodies and antigens, HDX-MS can help researchers re-engineer proteins to optimize their safety, efficacy, stability, and ability to be manufactured. This could include identifying antidrug antibody binding epitopes on therapeutic proteins, showing where proteins change shape

Table I. Benefits and disadvantages of common high-resolution techniques.

<table>
<thead>
<tr>
<th>Technique</th>
<th>Benefits</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| X-ray crystallography     | • Can characterize complexes at high resolution and show binding interactions at atomic level  
• Provides useful details about binding interactions to guide drug development  
• Is not affected by size | • Requires high-quality crystals of complexes, which can be difficult to obtain  
• Crystals may not always represent the functional form of the molecule  
• Limited by post-translational modifications |
| Nuclear magnetic resonance| • Can provide atomic-level detail in solution, which is more physiologically/pharmacologically relevant than crystals  
• Can identify binding interactions and conformational changes quickly once data are assigned  
• Amenable to analysis in diverse conditions/formulations | • Assigning data can be challenging, especially with larger molecules such as monoclonal antibodies  
• Limited by size  
• Requires stable isotope incorporation |
| Cryo-electron microscopy  | • Can examine shapes and structures of large, heterogeneous complexes  
• Can show orientation between associated proteins in complexes and aggregates | • Medium resolution  
• Potential to be altered with surface interactions |
| Mass spectrometry         | • Can be used with highly diverse biologic species having a broad range of properties (e.g., size, glycosylation/modifications, structure, shape)  
• Robust and fast analysis compared with other high-resolution techniques  
• Compatible with complex mixtures  
• Peptide-level and higher resolution | • Adding dimensions increases time required for analysis |

of properties (see Table I). These may be homogenous samples or individual components in heterogeneous or complex mixtures. MS is usually performed at peptide-level resolution, but the resolution can be made even higher by using tandem MS (MS/MS) or multidimensional MS (MSn) to further probe specific features of individual peptides. While this process takes longer and uses more resources, it does provide more detailed information on complex systems, including those that are not amenable to detection using X-ray crystallography or NMR.

The benefits of mass spectrometry approaches include:

- Showing how multiple target-drug interactions relate to function/MoA. For example, characterizing valency and binding for mAbs/bispecifics
- Elucidating interactions between drugs and the immune system
- Understanding the impact of glycosylation or other modifications on biologic drug stability as part of the CMC decision-making process
- Identifying changes in the biologic drug in different conditions, in complexes, and comparability before/after scale-up to support CMC decisions
- Analyzing synergy and compatibility among therapeutics to aid candidate selection, development, and CMC decisions to support personalized medicine.
Table II. Mass spectrometry (MS) approaches for characterizing binding.

<table>
<thead>
<tr>
<th>MS approach</th>
<th>Purpose</th>
<th>Information provided</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogen-deuterium exchange MS</td>
<td>Epitope mapping</td>
<td>• Reliably applied to diverse proteins and complexes: o Large, non-globular, flexible o Heavily glycosylated o Identifies regions involved in binding interactions o Identifies regions that undergo conformational change on binding</td>
<td>• Identify sites of target engagement by therapeutic o Assess changes to target induced by binding o Assess anti-drug antibody epitopes for personalized treatment</td>
</tr>
<tr>
<td>Native MS</td>
<td>Stoichiometry of complexes</td>
<td>• Exact mass unambiguously identifies number and types of subunits in large complexes o Analysis of solution state o Assess binding of competing species o Distinguish homo- versus heterodimeric bispecific mAbs</td>
<td>• Determine whether formed complexes support intended mechanism of action (MoA)</td>
</tr>
<tr>
<td>Combined</td>
<td>Improve decision-making</td>
<td>• Potential for informing MoA and efficacy o Co-engagement o Valency o Oligomerization o Identify potential synergies and competition o Combine therapeutics o Assess displacement by native ligands o Assess immune complex structures for potential immune reactivity</td>
<td>• Improve efficacy o Optimize dosing o Understand bioavailability and activity o Reduce counter-productive clearance o Improve stability and reduce aggregation o Reduce potential immune reactions o Enable re-engineering for better optimization and creation of biobetters</td>
</tr>
</tbody>
</table>

upon binding, or highlighting hot spots for aggregation.

Native MS techniques can be used to characterize stoichiometry of non-covalent complexes. By combining this with HDX-MS, researchers can understand more about target engagement and therefore improve candidate selection and optimization, thereby de-risking the development of biologic drugs.

COMBINING THE APPROACHES

While individual approaches can provide a lot of useful data, using a combination of techniques has additional benefits. For example, data from low-resolution approaches can be interpreted much more accurately in the context of high-resolution data. There are significant opportunities offered by using combined HDX-MS and native MS approaches to interpret accurately low-resolution data from high-throughput methods. This allows researchers opportunity to improve development from candidate selection through to manufacturing approaches.

CONCLUSION

Strategic application of advanced HDX-MS and native MS techniques, alone and in combination with each other and with other analysis approaches, can improve the identification of potentially successful biologic drugs and de-risking CMC and clinical designs earlier. Detailed assessment of target engagement using these techniques may provide useful guidance for better decision-making in biologic development programs.

REFERENCES

Cell and Gene Therapies — Contin. from page 13

may have an advantage in being able to scale up or down, to adapt to changes in demand.

“People have succeeded with therapeutic production at small scale, but we don’t have industrial experience yet. All stakeholder groups must come together to share experiences and identify ways to retire risk, reduce costs, keep up with regulatory pace, and make safe and effective products available to patients who need them,” Vanek says. “The pace of change and approvals is faster in this sector than we’ve ever seen before. Everyone is figuring this out as we go,” he says.

REFERENCES

Clinical Trial Manufacturing — Contin. from page 35

distribution site now becomes a pharmacy dispensing site. In the United States, the regulatory and licensing requirements for establishing a pharmacy and licensure in all 50 states must be met before patients can be supplied. This requires licensure and expertise in areas that have not traditionally been required at clinical supply facilities. In addition, shipping directly to patients requires that patient data privacy laws be followed. With traditional supplies, materials are shipped by kit number to a clinical site so that patient names or addresses are never part of the clinical supplier chain. In direct-to-patient, however, the established pharmacy will have this information, but must control it appropriately. There is also a need for greater flexibility, since not every patient will always require home shipment. For instance, the initial visit may need to be with the investigator, with subsequent shipments made to the patient’s home. Having materials co-located in one site with the ability to ship to the investigator’s site or directly to patient is important when the amount of available supply is low.

In addition, direct-to-patient orders will need to be flagged differently through the IRT and processed differently through the site. When establishing the trial setup, careful thought must be given as to whether an order should be triggered as a site shipment or a direct-to-patient shipment. In addition, care must be taken not to include patient names or addresses in the IRT request. The shipping site will need to have processes in place to split orders based on their intended destinations and to maintain patient record privacy standards. Finally, courier delivery is extremely important in direct-to-patient distribution, and drivers need additional training, particularly in interacting with patients so that confidentiality is maintained.

BioPharm: How do you work with sponsors on packaging to ensure the accuracy of blinded studies?

Blume (Catalent): Project documentation and sponsor communications are critical, especially with smaller companies, when CMC experts are performing manufacturing planning and clinical packaging planning with the vendor, working with the internal clinical team, and filing regulatory documentation.

It is crucial to ensure that the project communication plan with the clinical supply vendor is clearly worded so that the individual who approves project documents and requests is blinded. This should be clearly indicated in the initial project documentation supplied from the vendor. In detailed project discussions with cross-functional teams, it is also a good idea to mention at the beginning of the meeting agenda that blinded individuals will be included on the call and that care should be taken to avoid revealing any details that could unblind them.

DESIGNING DRUGS FOR THE COLD CHAIN

BioPharm: To what extent do you see logistics concerns being factored into drug development (i.e., regarding product stability).

Blume (Catalent): An increasing number of new products require tighter controls and lower handling temperatures. Starting the distribution and supply conversations as early as possible in the planning phase allows for planning of shipping and storage solutions that will take into account whatever stability profile is available for the product.
The Versatility of High Throughput Dynamic Light Scattering in Protein Characterization and Formulation Development

LIVE WEBCAST: Tuesday, August 20, 2019 at 11am EDT | 8am PDT | 4pm BST | 5pm CEST

Register for this free webcast at www.biopharminternational.com/bp_p/versatility

EVENT OVERVIEW:
This webcast will cover the versatility and utility of dynamic light scattering (DLS) in therapeutic protein characterization and formulation development. Through a series of case studies, the presentation will highlight the multiple ways of using the DynaPro Plate Reader III DLS plate reader to study protein stability, protein-protein self-interactions, and in the selection of optimal formulation conditions.

Key Learning Objectives
- Learn how isothermal DLS monitoring of protein formulations can rank stability (unfolding and or aggregation) and compliment other biophysical methods such as DSC
- Discover the use of thermal ramp DLS to monitor the stability of multiple protein formulations in a single experiment
- Discuss the integration of DLS experimentation into formulation development workflows
- Learn about the use of protein concentration dependent DLS to probe protein self-interaction

Who Should Attend
- Protein pharmaceutical and biotechnology scientists
- Protein engineers
- Formulation development scientists
- Biopharmaceutical process developers

Presenter
Katherine E. Bowers, PhD
Principal Scientist Group Leader
Fujifilm Diosynth Biotechnologies U.S.A., Inc

Moderator
Rita Peters
Editorial Director
BioPharm International

For questions contact Martha Devia at MDevia@mmhgroup.com
PRODUCT SPOTLIGHT

ONEBIO℠ SUITE: INTEGRATED BIOLOGICS DEVELOPMENT AND SUPPLY
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BIOBALL is a small water-soluble ball containing a precise number of microorganisms delivering unprecedented accuracy for quantitative microbiological quality control. BIOBALL is easy to use and requires no preparation or pre-incubation and is an accredited reference material under ISO Guide 34 standards.


DISTEK, INC.
Distek, a manufacturer of laboratory testing instruments for the pharmaceutical and biotechnology industry, has added a dual impeller single-use bioreactor (SUB) system to its BÎone portfolio. The new SUB increases mixing efficiency within the bioreactor, resulting in an increased mass transfer coefficient while maintaining the same rate of agitation.

Distek, Inc., 121 North Center Drive, North Brunswick, NJ 08902,
tel: 732.422.7585, bione@distekinc.com, www.distekinc.com

NGC PLATFORM
The NGC platform has evolved to meet the changing requirements of chromatographers and now includes ChromLab Software version 6.0 to address the needs of high-throughput labs with features that enhance total control and ease automation of the most complex purification workflows. Multivariable scouting allows numerous parameters to be evaluated within a method while also maximizing sample throughput. Bio-Rad Laboratories Inc., bio-rad.com/NGC

Microbioreactor System
Sartorius Stedim Biotech’s Generation 2 ambr 15 cell culture microbioreactor system offers increased flexibility and expanded capability for clone selection, media and feed optimization, and early process development work. The system replicates laboratory-scale bioreactor performance at the 10–15 mL microscale and controls up to 48 single-use bioreactor cultures in parallel.

Features include new functionality and a one-year license of the company’s clone selection software. Election of clones, media, and feeds can be performed under perfusion mimic conditions to bleed large volumes of culture and quickly remove spent media from the microbioreactors. A flexible workstation layout and an expanded tip bin capacity provide greater operator walk-away time, according to the company.

New culture passage steps and rapid vessel drain functionality allow for the adaptation of cell lines to different media for media screening studies to be performed in the microbioreactors. New media mixing steps automate the creation of media blends, eliminating the need to pre-mix. Rapid vessel drain functionality for automated cell passaging and media exchanges in the microbioreactors supports cell and gene therapy applications. A new culture station design provides lower stirrer speed control suitable for more sensitive cell lines.

Sartorius Stedim Biotech
www.sartorius.com

Plate Reader Offers Real-Time Detection and Analysis
Tecan’s Spark Cyto cell plate reader offers real-time detection and analysis of biological, chemical, and physical events while consistently capturing the maximum amount of data from every well.

The device combines the flexibility of a high-end multimode plate reader with whole well imaging and comprehensive environmental control for cell-based assays. Capable camera components and a patent-pending LED autofocus system provide real-time data acquisition and analysis for 6- to 384-well formats.

The reader allows qualitative and quantitative information to be integrated into multiparametric data sets, delivering insights faster than previously available, the company states. With three magnification levels and four acquisition channels, the device enables entire cell populations to be investigated by capturing the whole well area of 96- or 384-well microplates in just one image without tiling or distortion.

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Quality risk management plans are important because they help improve a company’s ability to provide quality product to patients. They are contingency plans with identified actions that help to ensure a continuous supply of product to the market that meets the expectations of being safe, effective, and available. They are dynamic documents that require integration into and data inputs from all departments in order to be successfully implemented at a company.

REFERENCE

1. ICH, Q9 Quality Risk Management (ICH, November 9, 2005). ◆

For more about quality risk management, visit BioPharmInternational.com to read the following:

• Essentials in Quality Risk Management
  www.biopharminternational.com/essentials-quality-risk-management

• Can QRM Transform Biopharmaceutical Operational and Quality Culture Excellence?
  www.biopharminternational.com/can-qrm-transform-biopharmaceutical-operational-and-quality-culture-excellence

Ask the Expert — Contin. from page 50

product. In this case, frequent shut downs can lead to product rejections, yield loss, and potential drug shortages. Once the risk has been identified and the impact evaluated, controls to mitigate the potential situation need to be identified and implemented. Some of the possible mitigation control strategies might include ensuring there are appropriate change parts for the line in inventory or plans to qualify the product production on a new more modern manufacturing line.

The last key element needed is data input and management. The data evaluated should be able to indicate if and when you need to employ one of your control strategies. In this simple scenario, an increase in down time on the line or a steady decrease in yield could be indicators that the manufacturing line is headed for a catastrophic failure and steps need to be taken to prevent a drug shortage situation.

The above discussion is only an example of a risk assessment in one area of an operation. Other areas of the process need to be evaluated for potential vulnerabilities and risk. These areas include an evaluation of the reliability of raw material suppliers, stability and compliance of contract suppliers (e.g., contract manufacturing organizations, contract test organizations), age and reliability of laboratory test equipment, etc. In other words, a solid, well-written and dynamic quality risk management plan will evaluate the overall organization, identify high-risk vulnerabilities, identify strategies for mitigation of the high-risk vulnerabilities, and rely on data to perform continuous monitoring of the vulnerabilities. And, of course, the plan will provide the appropriate documentation and rationale for the decisions.

Implementing a quality risk management plan in an organization can also be challenging. It needs to be introduced and discussed with all applicable function personnel involved in the operations including, but not limited to, finance, manufacturing, regulatory affairs, purchasing, auditing, and senior management. The plan should be dynamic and should be modified as situations change.

Let’s say you produce a product and you have a single-source supplier for one of your excipients. You have audited the supplier and have identified some significant gaps in their quality system. You identify this vulnerability in your quality risk management plan and indicate it is a high-risk item because of the lack of compliance of the excipient vendor. One of your mitigation strategies might be to qualify an alternate supplier for the excipient. Once you have qualified that alternate supplier, you need to update your plan to downgrade the risk because you have taken the appropriate steps to mitigate it and eliminate the identified vulnerability.
Quality Risk Management Plans
Create Effective Quality Systems

Quality risk management plans provide identified actions to ensure a continuous supply of safe and effective drug products, says Susan J. Schniepp, executive vice-president of post-approval pharma and distinguished fellow, Regulatory Compliance Associates.

Q: I am in the quality assurance department at my company. We are a small start-up, and one of my jobs is to develop a quality risk management plan. Can you give me some advice on what I need to consider when putting this plan together?

A: A well-written and well-implemented quality risk management plan is an integral and valuable element of an effective quality system. During the development and manufacturing of pharmaceutical products, the bottom line is that things can and will go wrong. The purpose of a quality risk management plan is to help ensure continued compliance with regulatory requirements, such as good manufacturing practices or good laboratory practices, when events occur during manufacturing that potentially impact patient safety and product quality.

International Council for Harmonization (ICH) Q9 states, “Two primary principles of quality risk management are: the evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and, the level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk” (1).

In developing your company’s plan, you will need to consider all aspects of the operation that impact the product. Managing your company’s risk with a well-defined plan may help reduce the activities associated with poor quality and inefficiencies associated with the product and the process, such as a reduction in deviations/investigations, scrap or wasted materials, customer complaints, and product yield.

The concept is to evaluate all aspects of the manufacturing process and identify areas of vulnerability. These vulnerabilities need to be assessed for their impact on the operation and the potential level of risk they pose. A well-written quality risk management plan is an ongoing process requiring rigorous documentation throughout the product lifecycle. It provides a solid rationale for how to improve efficiency and spend resources on the important activities to improve product quality rather than on low-risk activities that have little to no impact.

There are four basic elements that should be included in a quality risk management plan. The first element is to perform an analysis of the identified risk associated with the operations. For example, if your product is being produced using an older manufacturing line, there is a risk that the line will experience frequent breakdowns.

The second step is to evaluate the risk in terms of its impact on your ability to supply a quality...
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