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10 Can Vaccine Development Be Safely Accelerated?
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Biopharma’s Leadership Role in a Pandemic

As the coronavirus pandemic unfolds, the bio/pharma industry must practice science over hype.

The coronavirus pandemic is sweeping around the globe at a rapid pace, forcing governments, regulatory authorities, healthcare systems, and the bio/pharma industry to take novel measures to address the crisis. Some public health officials and doctors sounded early alarms about the spread of a novel coronavirus—severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—in January 2020; however, many people and governments did not heed the alarms or were slow to respond to the spread of coronavirus disease (COVID-19).

As politicians weigh protecting public health versus the impact on the economy, medical professionals beg for adequate supplies of face masks and ventilators. Meanwhile, many drug companies and research organizations have announced R&D efforts to test approved therapies as treatments to minimize the effects of COVID-19. The research focus of drugs in development have been redirected to target coronavirus symptoms. And, groups around the world have accelerated efforts to develop much-needed vaccines.

Following initial criticism for delays in approving diagnostic testing to detect who had the virus, FDA stepped up its activity, issuing more than a dozen guidance documents in March 2020. Actions included issuing emergency authorizations for diagnostic test and ventilators, easing regulations for remote monitoring of patients and clinical trials; allowing the compounding of hydroxychloroquine sulfate under certain conditions, releasing guidance for the preparation of hand sanitizers, and facilitating access to COVID-19 convalescent plasma for use in patients with life-threatening infections (1).

The immediate goal is to “flatten the curve” of new cases of COVID-19 to reduce strain on the healthcare system. Staying home, avoiding crowds, and washing your hands are simple measures we all owe the medical professionals, first responders, grocery store clerks, delivery services, transportation workers, and others on the front lines of maintaining our basic needs to get through this crisis.

Obviously, these non-pharmaceutical measures are only part of a temporary solution; therapies are desperately needed to treat COVID-19 patients, and vaccines ultimately required for long-term control of the virus. Bio/pharma researchers, development and manufacturing professionals, and companies supporting drug development and manufacturing are essential to these efforts.

At the same time, patients still need effective, affordable therapies to treat chronic diseases, cancers, and other conditions. A reliable drug supply is vital to maintain health and alleviate public concerns.

During the past few weeks, we have learned about many drugs and vaccines as potential cures. The world could use a “magic pill” right now. But drug developers know the challenges of working the science and producing the data to ensure that the therapy is safe and efficacious. One challenge for those in the bio/pharma industry is to avoid using excessive hype about a potential therapy, which can create false hope. Now is the time to lead with the message that science—not hopes or gut feelings—should drive all healthcare decisions.

The BioPharm International team thanks those working to develop new treatments and vaccines and those maintaining the drug supply; we are here to support those efforts. In addition to our normal coverage, we offer added coverage of COVID-19 drug development programs, links to research, industry suppliers, and regulatory updates. You can find the latest news, updates, and access to an archive of previous issues on www.biopharminternational.com.

Stay safe, and we wish you success in your drug development efforts.

Reference
Survey of peptide quantification methods and comparison of their reproducibility: A case study using oxytocin

Chenabling Li, Siratam Bhavara, Marie-Pier Thibeault, Jeremy Melanson, Andreas Blomgren, Torgunn Rundlof, Erik Kilpatrick, Carolyn J. Swami, Timothy Rudi, Yves Aubin, Kevin Grant, Margaret Butt, Wai Lok Shum, Tureson Kerim, William Sherwin, Yukari Nakagawa, Sergio Pavlin, Silvia Arrutia, Tim Wietl, Annina Picta, Dinesh Chalasan, Stephen Wulfish, Fouad Attou

In addition to USP, 14 laboratories in 10 countries representing industry, government, metrology and standard-setting organizations collaborated in this effort

Study focused on three analytical approaches:
- HPLC assay
- Quantitative nuclear magnetic resonance (qNMR)
- Amino acid analysis (AAA)

These methods were compared for their suitability with the nonapeptide oxytocin.

See the latest about use and suitability of three distinct analytical methods for peptide quantification: HPLC, qNMR and AAA. Published article can be downloaded from https://www.usp.org/biologics/peptides

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The 10th anniversary of the enactment of the Biologics Price Competition & Innovation Act (BPCI) in March 2020 has focused attention on the advances made over the past decade and main challenges ahead. Despite general disappointment over the slow pace of consumers gaining access to less costly biotech therapies, new FDA guidance and clarified policies provide added support for biosimilar development and approval, particularly for diabetes treatments. FDA also has teamed up with the Federal Trade Commission (FTC) to counter anticompetitive practices that thwart development and raise concerns about biosimilar safety and effectiveness.

A positive sign is that the pace of FDA approvals of biosimilars has picked up in recent months, with more than 26 approved products as of early February 2020—10 approved in 2019—and more than a dozen competitors on the market. In addition, the World Health Organization has begun to prequalify biosimilar versions of “essential medicines” to make these treatments more available and affordable in less developed countries.

INSULIN COMPETITORS

An important FDA initiative aims to encourage manufacturers to prepare the data needed to support applications for follow-on versions of insulins now deemed to be licensed as biologics and thus eligible for competition from biosimilar or interchangeable therapies. In February 2020, FDA issued a final rule defining the new process, as established by the BPCI and revised in legislation to clarify that the deeming process applies to insulin, human growth hormone, and most proteins—specifically any alpha amino acid polymer with the specific, defined sequence greater than 40 amino acids in size (1). The new rule aims to “bring down prices and help patients have access to more choices for these life-saving drugs,” said FDA Commissioner Stephen Hahn. FDA also issued explanatory documents for consumers (2) and physicians (3) to clarify that treatments approved under the new program will be just as safe and effective and accessible as brand insulin reference therapies.

Efforts to bring insulin competitors to market builds on FDA guidance issued in November 2019 outlining a streamlined development pathway for these long-established therapies (4). That advisory proposes reduced clinical immunogenicity studies for products that present strong comparative analytical assessments demonstrating high similarity to the reference drug, and no residual uncertainty regarding immunogenicity. In May 2019, FDA provided detailed advice on designing and evaluating such analytical studies and on providing scientific and technical information for the chemistry, manufacturing, and controls (CMC) portions of an application for a biosimilar in draft guidance (5). At that same time, FDA published long-awaited guidance on developing interchangeable biosimilars, again noting the importance of analyzing critical quality attributes and identifying analytical differences between the reference product and the proposed interchangeable (6).

MISINFORMATION CRACKDOWN

The FDA–FTC initiative further aims to encourage prescribing and reimbursement for biosimilars by taking aim at “misinformation” campaigns backed by brands to discourage biosimilar uptake. The regulators outline how they will work together to promote competitive markets for biological prod-
ucts that “contribute significantly to drug costs,” noted Commissioner Hahn (7).

The two agencies also offered to help biosimilar makers gain ready access to samples of reference products needed to develop and test follow-ons—a difficulty that also has plagued the broader generic-drug industry. And FTC is taking a close look at patent settlement agreements involving biologics and biosimilars to detect any antitrust violations. A joint public workshop held on March 9, 2020 addressed these efforts and other strategies to build a more competitive market for biological products.

In a related move, FDA also published guidance in February 2020 outlining the process for seeking FDA approval of a subset of approved indications of a reference product. This approach applies when patent and exclusivity provisions may prevent a newly licensed biosimilar from including all indications of a reference product on the label, a situation that often involves pediatric or orphan disease treatments. But once those limitations expire, FDA encourages the follow-on manufacturer to file a supplemental application with data supporting the expanded uses, as seen in an advisory outlining how data and labeling should be presented to add previously omitted conditions of use (8). FDA says it will review such supplements within six months, much faster than the usual 10-month timeframe set for supplements to biologics license applications (BLAs).

And to ensure that promotional messages related to biosimilars by both brands and competitors are truthful, non-misleading, and balanced, FDA draft guidance issued Feb. 3, 2020 instructs brands to avoid implying in its messages that a reference product is safer or more effective than an approved biosimilar, or that the follow-on is “not highly similar” to the reference product, even if the competitor is not licensed for all indications (9). The guidance emphasizes that a biosimilar product is not required to be identical to the brand to be licensed, but just that it be “highly similar” and without “clinically meaningful differences” in terms of safety, purity, and potency. An added proposal is that the FTC take antitrust action against brand manufacturers that make misleading claims to counter competitions.

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Can Vaccine Development Be Safely Accelerated?

Biopharma companies responding to the COVID-19 outbreak think accelerating the development of vaccines is safe.

CYNTHIA A. CHALLENER

Human coronaviruses (HCoVs) in the past were considered to cause nothing more than the common cold in healthy people. That changed with the advent of severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) in the past decade. The latest coronavirus—2019-nCoV, since renamed by the World Health Organization as COVID-19—emerged in December 2019 in Wuhan, China. As of late February 2020, it had sickened tens of thousands and killed nearly 3000 people.

Four of these large, enveloped, positive-strand RNA viruses are endemic globally and thought to cause 10–30% of upper respiratory tract infections in adults (1). They possess a surface spike (S) glycoprotein that binds to host cell receptors, and the nature of this protein is believed to determine the main properties of each coronavirus. SARS-CoV was the first coronavirus to jump from animals to humans; MERS-CoV and COVID-19 have as well.

The genetic sequence for COVID-19 was released to public databases on Jan. 10, 2020 by the Shanghai Public Health Clinical Center & School of Public Health (1). The three-dimensional (3-D) structure of the spike protein suggests that it binds more tightly to human cell surface receptors than SARS-CoV, a possible reason that this coronavirus exhibits greater infectivity (2).

Platform diagnostic methods have been rapidly adapted to include COVID-19 for early identification of cases. Several academic and industrial researchers have also focused on applying novel vaccine development and manufacturing platforms to the accelerated development of a COVID-19 vaccine.

In terms of vaccine development and protection against dangerous viral pathogens, there is nothing particularly unique about coronaviruses, according to Eric von Hofe, chief scientific officer of NuGenerex Immuno-Oncology. “All of the recent potentially pandemic viruses, including SARS and MERS and two flu viruses (avian and swine flu), have the common feature that they simply had never been seen before by the human immune system. That said, we now know a lot...”

CYNTHIA A. CHALLENER, PhD, is a contributing editor to BioPharm International.
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about how the human immune system protects against viral infections and can rapidly identify the critical parts of a new virus to target for vaccine development,” he says.

**PLATFORM TECHNOLOGIES ARE IDEAL FOR DEVELOPMENT**

Traditional vaccines, like the seasonal flu vaccine, are made by growing up large quantities of the virus and in some way killing or inactivating it so that it can be used safely as a vaccine. This approach is an old technology from the middle of the past century, according to von Hofe. “The main problem here is the time it takes to produce the vaccine, which is at least a year and can be several. Ideally, we’d have a platform technology that could be used to produce a vaccine in a few months,” he observes.

Such technology platforms should be flexible enough to respond to any new viral threat. “We would like to have a simple ‘plug-and-play’ setup where the critical components of a new virus required to make the vaccine can be determined by rapid computer analysis and plugged into the platform to generate a vaccine,” von Hofe notes. “Getting all of the critical components produced and structured in a way that perfectly models the vaccine is the big challenge,” he adds.

**A REDUCTIONIST APPROACH IS BEST**

The best way, von Hofe says, is to follow a reductionist strategy to identify key viral components that alone produce complete protection in a safe vaccine that can be manufactured rapidly and in a cost-effective manner. “Clearly this is a tall order, but we’re making good progress in that direction,” he asserts.

As an example, von Hofe points to the development of subunit vaccines that rely on recombinant DNA to encode a critical subunit of the vaccine that generates a response. There are additional challenges to this approach, however. “While responses can be produced, the protection may be short-lived, as there is no guarantee that immunological memory will be generated as is possible with a whole virus vaccine,” he comments.

**THE DNA APPROACH AGAINST COVID-19**

Inovio Pharmaceuticals is one company developing a DNA-based vaccine against COVID-19. The biotech was the first to advance a vaccine (INO-4700) against MERS-CoV into human testing and is currently preparing to initiate a Phase II trial for INO-4700 in the Middle East. This vaccine, however, cannot be used against COVID-19 because the two coronaviruses are too different.

To develop a new vaccine, Inovio first converts the virus’ RNA into DNA and identifies short sections that will, according to computer simulations, generate the greatest immune response. The plasmids are then produced in large quantities using bacteria. The overall development and approval timeline is thereby significantly reduced.

Inovio began animal testing of INO-4800, its COVID-19 vaccine candidate, in February 2020 and is aiming to begin human safety testing in early summer 2020. The company will conduct tests in both the United States and China, the latter in collaboration with Beijing Advaccine Biotechnology Co. (3). Work in the US is supported by a $9-million grant from the Coalition for Epidemic Preparedness Innovations (CEPI). The collaboration with Beijing Advaccine is anticipated to accelerate developed on INO-4800 in China by providing access to not only its vaccine expertise, but also its relationship and experience with Chinese regulatory authorities and clinical trial management in the country.

**PROPHYLACTIC MESSENGER RNA VACCINES**

Two companies, both also supported by grants from CEPI, have developed platform technologies based on messenger RNA (mRNA). Cambridge, MA–based Moderna—which has developed numerous prophylactic mRNA vaccines with positive Phase I clinical readouts and also has a fully integrated clinical–material manufacturing site—is progressing its COVID-19 vaccine candidate (mRNA-1273) into the clinic (4, 5). The Vaccine Research Center (VRC) of the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), collaborated with Moderna to design the vaccine. NIAID will conduct investigational new drug-enabling studies and a Phase I clinical study in the US.

Moderna’s mRNA vaccines can contain multiple mRNAs coding for different proteins and mimic natural infection, thus stimulating a more potent response, according to the company. Only the coding region of the mRNA must be changed for each new vaccine. The rapid discovery approach and the manufacturing agility of mRNA vaccine design and production also make it an effective platform technology.

Just 42 days after sequence selection, Moderna shipped the first batch of mRNA-1273 to NIAID for use in a planned Phase I clinical study in the US. The mRNA vaccine encodes for a pre-fusion stabilized form of the COVID-19 S protein.

German biotech CureVac also has an mRNA platform technology for vaccine development and manufacturing suited for rapid response to viral outbreaks, it says (6). Using an extensive in-house nucleotide sequence library, CureVac is able to identify optimum sequences for any given vaccine target and eliminate the need for chemical modification, shrinking the development timeline.

The company has also developed specific carrier molecules for its mRNA products, including lipid nanoparticles (LNPs), developed in partnership with Acuitas Therapeutics and Arcturus Therapeutics). It is developing The RNA Printer, a mobile, automated pro-
A fourth group receiving funding from CEPI for application of a vaccine platform technology to accelerated development and manufacture of a COVID-19 vaccine is located at Australia’s University of Queensland (UQ) School of Chemistry and Molecular Biosciences (7). Its rapid response technology relies on molecular clamp technology, an approach developed by UQ researchers and patented by UniQuest.

The molecular clamp technology is used to create subunit vaccines against class I and III enveloped viruses by stabilizing the pre-fusion form of viral fusion proteins, thus mimicking the protein conformation found on live virus and generating a strong immune response. A polypeptide is used to maintain the pre-fusion structure and prevent the protein from folding after entry into the cell.

The platform technology, which does not require prior knowledge of a protein’s quaternary structure, therefore facilitates the expression of recombinant viral glycoproteins without loss of native antigenicity (8). It has previously been used to produce chimeric polypeptides that mimic the pre-fusion conformations of several enveloped viruses. The goal is to complete preclinical development within 16 weeks and then progress directly to Phase I clinical trials, with completion of that step in 10 weeks, followed by large-scale production of more than 200,000 doses in eight weeks.

For its COVID-19 vaccine, the UQ researchers created a first candidate in the laboratory in just three weeks (9). This work confirmed that the engineered vaccine candidate is readily recognized by the immune system and triggers a protective immune response. Plans for preclinical testing were underway as of late February 2020, and the researchers hope to begin clinical testing by mid-2020.

**LEVERAGING COMPUTER TECHNOLOGY**

NuGenerex Immuno-Oncology is focusing on what von Hofe refers to as the smallest and simplest fragments of the virus needed to produce an immune response. These short fragments of proteins are identified by a computer algorithm and can be made rapidly by entirely synthetic means. They are modified to ensure that they activate immune cells that are key in producing immunological memory. “While these virus fragments may not produce as complete a response as whole inactivated viruses, they basically produce a ‘memory’, so when a person treated with our vaccine does encounter the virus, he or she is more prepared to mount an effective response,” von Hofe explains. The technology is also a platform approach because it can be applied to virtually any virus that may emerge as a threat.

**BIG PHARMA HAS PROGRAMS, TOO**

While these smaller biotechs have generated attention for their accelerated development platforms, Big Pharma companies have also been actively working on COVID-19 vaccine candidates. Both Johnson & Johnson and Sanofi are collaborating with the US Department of Health & Human Services (HHS). Johnson & Johnson’s Janssen Pharmaceutical Companies unit is collaborating with the HHS’ Biomedical Advanced Research and Development Authority (BARDA) to rapidly advance the initial stages of Janssen’s COVID-19 vaccine development program, which is based on its AdVac and PER.C6 platform technologies (10). BARDA is funding accelerated development of a candidate into Phase I clinical trials, while Janssen is upscaling its manufacturing capacities.

Sanofi Pasteur, the vaccines global business unit of Sanofi, is also collaborating with BARDA, using its established recombinant DNA technology platform to accelerate the development of a potential COVID-19 vaccine (11). This technology produces an exact genetic match to proteins found on the surface of the virus, which are then expressed using Sanofi’s insect (baculovirus) expression platform. The technology is used for Sanofi’s licensed recombinant influenza vaccine and a SARS vaccine that has been shown in non-clinical studies to be immunogenic and afford partial protection in animal challenge models.

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Decades ago, bioreactors were little more than the vessels in which fermentation or cell culture took place. Each bioreactor was a bit like a black box, as developers focused on process measurements that would keep cells viable and boost output. As their efforts have shone more light on the biopharma design space, the bioreactor is no longer viewed as a black box, but an integral part of a much larger interactive ecosystem. On the very front end, cell-line and antibody expression platforms have reduced the time required for cell-line development and antibody expression, with some platforms reported to reduce the time required from months to days (1). Knowledge of processes, cells, and media and their interaction has led to process improvements, but also improvements in bioreactor design, and virtually redefined upstream productivity. “We’re seeing a significant shift in what we consider normal productivity for a protein biological process,” says Patrick Gammell, executive director for process development at Amgen.

Results are being seen upstream, in improved single-use bioreactor systems. Once used exclusively in research settings, single-use systems have become entrenched in the late development scene, as data showed their potential to boost production capacity (2). As designs improved, the contract development and manufacturing organization (CDMO) Lonza Pharma and Biotech became an early adopter of single-use systems for Phase II and III programs, says Atul Mohindra, Lonza’s R&D director for biomanufacturing.

Another major trend is the widespread use of process intensification (e.g., the application of perfusion to boost cell density). Bioreactor design efforts continue to focus on integrating spectroscopy and better sensors and to improve process control. Over the next few years, experts predict a focus on single-use bioreactors better designed to handle the higher cell densities that result from perfusion, by offering improved mixing and oxygen transfer (3).

At Millipore-Sigma, says Darren Verlenden, the company’s head of bioprocessing, one area of focus in bioreactor development is in new sparger and impeller designs. Their goal is to improve the volumetric mass transfer coefficient, KLa (a measure of the rate of oxygen used for fermentation) and mixing so that the bioreactors will be better able to handle increased cell densities.

Bioreactors Redefine Upstream Productivity

New bioreactor designs, coupled with better media, process intensification and analytics, continue to improve upstream bioprocessing.

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REDDUCING SHEAR
Another focus will be optimizing shear and improving cell retention, through use of fixed-bed bioreactors and other technologies (3). To meet these goals, Pall offers the iCELLis fixed-bed bioreactor as well as the Cadence product line, which incorporates acoustic wave separation technology, designed to improve cell retention without increasing shear.

Also using the fixed-bed approach is a hybrid single-use bioreactor design developed by Univercells, which links a structured fixed-bed bioreactor to an automated tangential flow filtration concentrator. This design reduces process footprint, processing time, and building and operating costs, according to product manager Alex Chatel. It also reduces the solid impurities sent for downstream processing, reducing the time and number of operations required to generate materials for downstream processing, he says.

Univercells has been focusing mainly on applications in vaccine development and manufacturing. In March 2020, it launched a new CDMO, Exothera, that will use its own as well as other technologies to develop viral vector processes for gene and cell therapies, with the goal of reducing costs and time to market. The company will perform this work at a 15,000-m² site in Jumet, Belgium.

In general, the industry is moving towards intensified, connected, and continuous bioprocessing, says Verlenden. GE Healthcare Biotech is updating its bioreactors to enhance process intensification (e.g., by introducing an automatic perfusion system that can be integrated directly into the Xcellerex bioreactor platform).

Upstream and downstream operations are being integrated more closely, and downstream bottlenecks addressed by technologies such as continuous capture chromatography and flow-through polishing tools and improved buffer and media preparation, says Verlenden. Currently, he says, the company’s customers expect that 40-50% of their processes will use continuous capture and flow through polishing technologies over the next five years.

ANALYTICS AND CONTROL
Improved analytics and control is also guiding new product development. Pall Life Sciences has incorporated supervisory control and data acquisition capabilities into its bioreactors, while Sartorius’ latest Biostat STR bioreactors incorporate automation and process analytical technologies, in an effort to simplify configuration changes for users, not only during development but also for manufacturing. GE Healthcare is using improved sensors, to help users better assess critical quality attributes (CQA) and aggregate the data sets that will be the basis for process modeling, the development of digital process twins, and use of artificial intelligence, according to Avril Vermunt, strategic technologies partners leader at GE Healthcare’s life-sciences division.

As understanding of the design space improves, the bioreactor is no longer a black box, but part of an interactive ecosystem.

Healthcare is using improved sensors, to help users better assess critical quality attributes (CQA) and aggregate the data sets that will be the basis for process modeling, the development of digital process twins, and use of artificial intelligence, according to Avril Vermunt, strategic technologies partners leader at GE Healthcare’s life-sciences division.

DESIGN ENHANCEMENTS
Amgen Corp. is putting many of these concepts into practice at a new facility in Rhode Island, which is expected to start up in 2020. Patrick Gammell, Amgen’s executive director for process development, shared insights with BioPharm International.

BioPharm: What are the most significant improvements you have seen in bioreactors within the past few years?

Gammell: Single-use bioreactors have evolved significantly in terms of design enhancements to drive leak-free robustness, mixing, and gassing improvements to allow these bioreactors to sustain long-term high-density cultures. A number of these enhancements have come as a result of the continued push within the industry to drive process intensification through improvements in cell lines, media formulations, and through the use of perfused formats.

In addition, the application of computational fluid dynamic modeling as well as other advanced modeling techniques has been instrumental in helping to optimize bioreactor design. These improvements in bioreactor and perfusion technologies (e.g., filter formats) have come from close collaboration between the manufacturers of biologic medicines and the single-use suppliers. A number of suppliers and academic institutions are also working on the potential to directly integrate sensor technologies into single-use systems to further dematerialize the process and ancillary equipment required for robust manufacturing. The outcome of all of the recent work on bioreactor optimization and, in particular, the use of modeling technologies is also driving improvements in the tech transfer and scale up of processes. Where, in the past, developers used to take a somewhat empirical approach to these efforts, the use of models allows us to digitally optimize prior to use with actual cells, and this practice continues to transform the way that we work today.

BioPharm: What overall improvements have been made in commercial-scale upstream bioprocessing?

Gammell: Over the past two to three years there have been significant improvements in terms of process
intensification resulting from technological advances across the lifecycle of the upstream process. Cell-line development and innovations in automated clone selection have had a great impact, along with the development of enriched nutrient media formulations. These formulations promote and then within living cells. This knowledge allows manufacturers to design process control strategies to ensure consistent and reliable product quality.

In addition to developments in upstream technologies, the continued advancement of high-throughput analytical product characterization has allowed us to better understand the regulation of how products are formed within living cells. This knowledge allows manufacturers to design process control strategies to ensure consistent and reliable product quality.

FUTURE INNOVATIONS

**BioPharm:** What will be key areas for innovation in the near future?

**Gammell:** Continuous manufacturing for biologics is an area of intense focus for many academic and industrial researchers, and creates new and interesting challenges for innovative thinking, in particular the challenge of integrating appropriate in-line analytical technologies in combination with complex multivariate model-based control systems to ensure that, over an extended process format, the process remains in a state of control and that product output remains consistent. A number of these individual components already exist today. The innovation will come from integrating them to ensure robust performance in a continuous format.

**BioPharm:** Is biopharm improving upstream-downstream integration?

**Gammell:** In the old paradigm, upstream process designers were focused on titer and did not necessarily consider the impact of upstream process design decisions on harvest operations or purification complexity or yields. A significant improvement came as a result of the application of the QTPP (quality target product profile) concept, which drives us to design products by starting at the patient and working backwards. The QTPP approach necessitates very careful integration from device designers, formulators, purification scientists, and upstream developers. This [collaborative] approach is key to an integrated process design strategy that has already allowed us to better integrate from upstream, through harvest and into purification.

The continued intensification of upstream processes in terms of cell densities and titer creates new opportunities for harvest/cell separation technology development, and the higher product concentrations also lead to challenges in terms of sizing the purification operations and how they are cycled. Continued research into higher capacity and cleanable purification resins will remain important.

**NEXT-GEN BIOPROCESSING**

**BioPharm:** What are Amgen’s plans for the new Rhode Island facility?

**Gammell:** The new biomanufacturing plant in Rhode Island will be structurally complete in 2020 and will use Amgen’s prove next-generation biomanufacturing capabilities to manufacture products for the United States and global markets. In contrast to conventional plants that leverage fixed bioreactors and tanks at scales of up to 20,000 L, next-generation manufacturing plants have adopted a flexible, modular design that leverage much smaller 2000-L vessels that are portable and accommodate single-use bioreactor bags.

These smaller, modular bioreactors can produce as much protein as the large stainless-steel tanks currently used at conventional plants. The impact of these innovations results in a 50% reduction in construction time and approximately one half of the operating cost of a traditional plant.

Next-generation biomanufacturing plants also offer greater environmental benefits. Within the plant, the equipment is portable and smaller, with a significant deployment of single-use components, which results in much greater flexibility and speed when manufacturing different medicines simultaneously.

**DATA MANAGEMENT**

**BioPharm:** Amgen recently started a project that aimed to improve digital data management for raw materials. How is that work progressing?

**Gammell:** Amgen has invested heavily in our data infrastructure to allow us to integrate all of our data sources, including process monitoring, sensors, equipment, and product testing via an enterprise data lake. This capability allows an unprecedented ability to detect and understand the sources of process and product variation.

A significant potential source of variation comes from raw materials, so Amgen has been working with suppliers such as GE to integrate supplier data with process and product data. This [integration] not only allows us to better understand and predict issues as a result of material variation, it also allows us to collaborate with key suppliers to continuously optimize and improve the consistency of our materials. Our goal is to continue to gain access to data sources, including data from the suppliers to our suppliers, which increases our understanding and, again, our ability to predict and prevent issues that may impair our ability to serve every patient every time.

**REFERENCES**


What’s New in Downstream Technologies

The latest advances in downstream technologies include a fluid chromatography system, sensing and control units for hygienic valves, a compact valve platform, a membrane purification column, and a protein A affinity chromatography resin.

LAUREN LAVELLE

As the biomanufacturing landscape continues to advance, downstream technologies are evolving to meet users’ needs. The following products have been developed to support the bioprocessing industry.

FLUID CHROMATOGRAPHY SYSTEM

Nexera UC Prep from Shimadzu and the Enabling Technologies Consortium (ETC) is a preparative supercritical fluid chromatography system (SFC) that provides semi-prep purification for the pharmaceutical industry (1). Built on the Nexera ultra high-performance liquid chromatograph platform, the system can be adjusted for user specifications to perform various purification functions including chiral or achiral purifications, single injections, stacked injections, and fraction collections from microliters to liters.

The system comes equipped with a combination injector/fraction collector, a carbon dioxide pump with a compact integrated chiller, a novel gas-liquid separator design for high recovery and low carryover, and preparative software for streamlining operations. Additionally, the SFC shortens purification run time and dry down time while eliminating the need for the solvents used in typical phase prep LC.

“The Nexera UC Prep system is an improved purification instrumentation that meets the specifications and requirements from SFC users across the pharmaceutical industry,” said Mirlinda Biba, PhD, principal scientist, Merck & Co. Inc., and ETC lead for this project, in a press release. “This new generation system provides improved hardware and software features that answer the pharmaceutical industry’s demand for an efficient and robust prep SFC system.”
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Updated Sensing and Control Unit for Hygienic Valves

Alfa Laval introduced an updated version of its second-generation valve sensing and control units for hygienic valves, the Alfa Laval ThinkTop V50 and V70 (2). The new addition, the Alfa Laval ThinkTop IO-Link, is a communication protocol for point-to-point communication between hygienic valves and automation systems via real-time data exchange, improved diagnostics, and simplified configurability and control.

Like the V50 and V70, the IO-Link is equipped with butterfly, single-seat, double-seat, and special valves to meet all valve requirements. Additionally, the new device includes M12 connectors and automatic recording of the hygienic valve stroke duration for faster installation time, the ability to assign priority to critical data, parameters that can be changed from a remote automation system, and data storage, availability, and analytics help for improved operations.

“Suddenly it’s easier to capture, store, analyze, and act upon meaningful data,” said René Stietz, product management Valves & Automation, Hygienic Fluid Handling, Alfa Laval, in the press release. “You get all the finesse of the newly reengineered Alfa Laval ThinkTop—and valuable benefits like more data, higher productivity, and higher yields.”

Compact Valve Platform

ITT unveiled a new addition to its EnviZion valve product line, the BioviZion, a fractional size valve for 0.25–0.5 in. applications that includes a mechanical thermal compensation system, a quick-change bonnet, and stainless-steel and patented diaphragm studs (3).

The platform features a 360° active seal protection for a leak-free operation that removes the risk of contamination and the need to re-torque after thermal cycling. It also provides less downtime, lengthier preventative maintenance cycles, and a larger production capacity for manufacturers.

“The unique EnviZion design has set a new standard for valves in the BioPharm industry,” said Dave Loula, global product director for ITT Engineered Valves, in a press release. “We have incorporated the same patented technology into a fractional size valve and added new features to overcome challenges related to dimensional limitations. This provides manufacturers with improved performance and reliability for critical sampling and low flow installations.”

Chromatography Column for Membrane Purification

The CIMmultus EV monolithic column from BIA Separations is a pre-packed chromatography column that works to eliminate non-exosomal vesicles and concentrate exosomes in a low shear atmosphere (4).

The column comes with sizable flow-through channels that are formulated to work with large proteins, viruses, virus-like particles, and pDNA as single-use disposable or multi-use columns (5). Additionally, the column is made of epoxy thermostet materials and carbon fibers, which gives it the similar strength and structure of stainless steel.

“Exosomes represent the next-generation delivery strategy for nucleic acids and other therapeutics, as well as being evaluated as a platform for regenerative medicine with high hopes of bringing more therapeutic options to chronically ill patients,” said Aleš Štrancar, CEO at BIA Separations, in a press release. “We are all looking forward to seeing the impact of our tools on this novel therapy space.”

Protein A Affinity Chromatography Resin

Avantor introduced the J.T.Baker Bakerbond PROchivA, a new Protein A affinity chromatography resin for the purification of antibodies during monoclonal antibody (mAb) production. The resin is used during the Protein A affinity chromatography step of mAbs manufacturing. It also works in conjunction with current manufacturing standards to guarantee stability in workflow processes and compliance protocols (6).

“Biopharmaceutical developers and manufacturers are urgently seeking new tools to drive more efficiency in their production processes. But they cannot compromise on quality standards as they work to provide powerful medicines to patients in a timely, safe, and efficient manner,” said Dr. Ger Brophy, executive vice-president for Biopharma Production at Avantor, in a company press release. “Our resin provides customers with a best-in-class, high-performing alternative to existing purification technology, with the benefit of greater supply chain flexibility and security.”

References


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Seeing Success with Single-Use Solutions

Single-use solutions continue to grow in popularity, largely as a result of the cost and time efficiencies they can afford biopharma companies.

FELICITY THOMAS

The market for single-use equipment within biopharma worldwide is expected to grow by a compound annual rate of 13.4% over the next five years (1). Growth in this market is expected to be driven by companies seeking more cost-effective solutions, the integration of single-use technologies in continuous processes, and the rapid advancement of biologics.

BioPharm International sat down with Johannes Kirchmair, managing director, Single Use Support; and Jon Van Pelt, general manager Bioprocess Single Use and Enterprise, GE Healthcare Life Sciences, to discuss the benefits, important considerations, and trends of single-use solutions in biopharma in more detail.

DESIRABLE PLATFORM

BioPharm: Single-use solutions have continuously increased in popularity over the years, could you elaborate on why these solutions are proving desirable and the benefits they afford users?

Van Pelt (GE Healthcare): The reality is that single-use is an established accepted platform within biopharma. The solutions afford biopharmaceutical manufacturers several benefits: The speed of changeover through the elimination of non-value-added steps, such as clean-in-place (CIP) operations or requiring sterilization-in-place, and the risk reduction of cross contamination between batches. These benefits translate into more efficiency and increased production capacity.

Kirchmair (Single Use Support): Single-use technologies address exactly the challenges the industry is facing with their development portfolio of products and in commercial manufacturing. During development, biopharma companies must be flexible with production floors potentially ready for a range of products and product classes. As a result of these requirements, single-use solutions prove beneficial because it is possible to mix several products in one set of hardware and it is possible to produce individual products cost-effectively.

Even if a company reaches the commercial scale, there is no guarantee that the product will perform once it is commercially available on the market. However, single-use solutions afford companies the flexibility to scale-up and scale-down production easily or use the same floor/set of hardware for another
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product if required. Furthermore, with a single-use contact surface, the number of qualification and validation exercises that are needed is reduced.

PROMOTING SUCCESS
BioPharm: How can single-use solutions promote increased success for companies within biopharma?

Kirchmair (Single Use Support): Through single-use solutions, biopharma companies can enter the market relatively easily. For example, some suppliers of single-use solutions offer end-to-end solutions where it is possible to receive a prequalified set of products from seed to fill/finish. Moreover, the use of single-use solutions in the contract manufacturing organization (CMO) space can give rise to rapid turnaround times and, hence, reduced costs. In general, I believe that by using single-use solutions, barriers, such as cost to bringing a molecule to clinic and market, are lowered.

Van Pelt (GE Healthcare): Speed-to-market is often cited by companies using single-use technologies. Single-use promotes efficient utilization of production resources particularly with process set-up time at all scales of operation. The ability to design a process flow from cell expansion to purification in reduced time, rapidly scale up to clinical, then convert to commercial production are governing success factors. These factors also contribute to a more timely use of capital funds as companies go through clinical trials, reducing financial risk.

POTENTIAL PITFALLS
BioPharm: Are there pitfalls that companies should be aware of when looking to implement single-use consumables within biomanufacturing processes?

Van Pelt (GE Healthcare): Unlike stainless steel, where you buy and use, again and again, you are in an ongoing relationship with your single-use supplier. You should assure security of supply (issues such as financial stability, robust supplier quality, mapping of supply risk); quality (issues related to a robust quality management system—corrective actions and preventive actions management and complaint management), technical expertise (issues such as robust product development, materials understanding; and manufacturing (issues such as manufacturing workmanship, rigor, and capacity). You should also understand single-use workflows within your facility; you should account for the need for large enough storage facilities to house sufficient inventory and for the waste management needed to process the used materials. Training is very important, as without this, people commonly experience higher failure rates related to improper installation and use.

Kirchmair (Single Use Support): Personally, I would advise never getting locked in with one consumable provider, because if something goes wrong with the supply chain, you are trapped. However, there are regulatory challenges that need to be considered. Filing for commercial products needs to be well thought out, for example, so it is possible to switch your primary contact layer even during the commercial phase. In my opinion, the future will be with single-use [bag] provider agnostic platforms, such as a bioreactor hardware that can handle bioreactor bags from several providers, or a freeze/thaw platform that is able to handle bags from several suppliers.

WASTE MANAGEMENT
BioPharm: What about waste management? Should companies be seeking extra measures in this regard?

Kirchmair (Single Use Support): Reusable systems are not really an option, in my opinion, but times are changing and environmental aspects should be considered by everyone, including the biopharma industry. In general, the environmental impact of single-use solutions is not too bad (several independent studies are showing that) but it’s still plastic! So, the suppliers have to help their clients to treat the waste properly to make sure that the impact is minimal. A global service platform to help companies manage waste would be an ideal solution—so, where waste is collected and treated in a professional way, similar to the disposal of confidential documents. This service platform could be an attractive business model and environmentally friendly at the same time.

Van Pelt (GE Healthcare): Sustainability is an area that has been on our radar for over 10 years. The first comparison of single use to stainless steel Life Cycle Assessment (“cradle to grave”) performed to the ISO 14040 standard concluded that single use was favorable from an environmental impact (2). The energy to fabricate reusable components and the utilization of thermal energy for sterilization and water for injection for CIP operations had a higher environmental impact versus single use.

However, the transport of single-use components is an area that should be studied more closely because transport is the largest contributor to the carbon footprint. Conversion of waste is another point for consideration. Plastic components, especially film, cannot be recycled other than as fillers for construction materials. Films are challenging because they are engineered composites of multiple layers consisting of different functional materials. Low extractable polyethylenes, oxygen barriers, tie layers all contribute to the final film that cannot be separated. Conversion to fuels is another possibility that is being pursued as a solution.

WORK IN STANDARDIZATION
BioPharm: Is there any work being done to standardize single-use solutions?

Van Pelt (GE Healthcare): Participation between suppliers and biopharma working groups such as BioPhorum Operations Group, ASTM International, and British Pharmaceutical Students’ Association provide a forum and are actively moving toward standardization frameworks.

Kirchmair (Single Use Support): There are a lot of good ideas in place, but ultimately the variety of products is
part of the single-use business model in the industry. Therefore, it is possible that there is not sufficient passion for standardization in industry. However, if there is an absolute need for standardization of single-use components, the pressure probably has to come from the end users to force it to materialize. Currently, it does not look like this pressure is coming. Standardization would lead to a smooth interaction between biotechs, the end-users, CMOs, and the suppliers. Obviously, standardization would be a desirable outcome as it would mean the industry would be able to collaborate more easily on a global scale.

ON THE HORIZON?

BioPharm: What trends do you foresee as being important in single-use solutions in the near future?

Van Pelt (GE Healthcare): A series of cascading trends are on the horizon in the near and longer term. Short-term, sustainability through passive inventory management will be linked to cloud-based information transmission that facilitates predictive, staged shipments while minimizing wasteful transport. Mid-term, single-use on-line/in-line sensor technology will lead to connected processing enabled by smart process control. Finally, long-term, the data obtained will then evolve to predictive process control through artificial intelligence algorithms.

The single-use industry will be instrumental in helping biopharma customers accelerate their path towards delivering advanced therapies to market as quickly and cost effectively as possible. This trait is especially true in the emerging areas of cell and gene therapy. In addition to delivering flexibility in scale and speed in operations, single-use providers and biopharma customers will need to work on streamlining the consumable design space for improved efficiency.

Kirchmair (Single Use Support): Big trends that will impact single-use solutions in the near future include automation, increased robustness, elimination of manual interaction, scale-up of more commercial processes, cell and gene therapy products, and essentially the industrialization of the single-use operation. Fully automated, online monitored, consumable provider independent platforms will be the future. That’s a natural evolution.

REFERENCES

Contamination Control for Cell Therapy

A variety of assays should be used to detect bacterial, fungal, and viral contaminants in the human source cells used for cell therapies.

FELIZA MIRASOL

Though cell therapy is a recent innovation, with the first therapies approved by FDA in 2017, the use of human cells has been a standard of care for decades in hematology and oncology (1). A cell therapy can be derived from a variety of sources, including hematopoietic, skeletal muscle, neural, and mesenchymal stem cells (i.e., adult stem cells that differentiate into structures such as connective tissues, blood, lymphatics, bone, and cartilage). Lymphocytes, dendritic cells, and pancreatic islet cells can also function as source cells. Many cell-based therapies currently in development are based on induced pluripotent stem cells (iPSCs), adult cells that have been genetically reprogrammed back into a pluripotent state (i.e., so that they can differentiate into one of many types of cells in vivo) (2).

There are two types of cell therapy: autologous and allogeneic. In autologous cell therapy, the source cells come from the patient to whom the therapy is administered. In allogeneic cell therapy, the source materials are cells from an independent donor, and the therapy can be administered to a number of patients.

Given the urgency of ensuring good patient outcomes, it is essential to have a strategy in place for preventing contamination of source cells, as well as the resulting cell therapies. Any biocontaminants found in critical zones of the cleanroom environment can endanger patients’ lives, and have a devastating impact on finances and reputation (3).

Maintaining an aseptic environment is critical to minimizing the risk of contamination from extrinsic sources. Intrinsic contamination risks also exist in the cell manufacturing processes, however, primarily due to the fact that the source cells cannot be sterilized. This can raise concerns over the risks of contamination as well as cross-contamination.

Contamination control over the manufacturing of a cell-based product requires mapping out the entire process (4). This approach helps developers and manufacturers understand the risks involved at each step of the manufacturing process. Having a proactive contamination-control mindset is key to mitigating risks in general.

“There are unique challenges in both allogeneic and autologous cell therapy production, given the human origin of the cells,” says Andrew Bulpin, head of process solutions, MilliporeSigma. In allogeneic therapies, these cells typically come from healthy donors, Bulpin points out, but there is a limit to how many doses can be grown from a single donation, given the limited number...
of times a cell can double. This introduces the need to address donor-to-donor variability in incoming material for therapeutic uses.

“Autologous therapies have the other extreme—each dose starts with the cells of the sick patient. This introduces supply chain challenges (i.e., harvesting, shipping from the patient, manipulating, shipping to the patient, and administering cells),” Bulpin adds. Care must be taken to ensure the chain of custody so that each patient receives his or her own cells. Adding to the complications is the variability in cell health from the patient, which demands that processing be extra robust.

CELL HEALTH ASSAYS
To assess cell health and the presence of any contamination in autologous or allogeneic therapies, a range of assays is required to test the source materials. According to Bulpin, this includes assays that are highly sensitive and specific to a particular target contaminant (e.g., polymerase chain reaction (PCR) assays), as well as assays that offer broad detection capabilities, such as next generation sequencing (NGS), in-vitro cell-based assays, and in-vivo assays.

“The choice of assay is influenced by a number of factors, including the ability of the contaminant to be cultivated in vitro or tested in vivo, but also the expectations of the regulatory agencies that will be reviewing the assay data,” Bulpin states.

PCR assays are used to detect mycoplasma and disease-causing viruses in both autologous and allogeneic source cells, Bulpin says, and they typically generate results in one to three days. A broader cultivation assay—based on a rapid, semi-automated method—is often employed for the detection of bacteria and fungi, and usually generates results in five to 10 days, he says. “Turnaround of these assays is time critical in delivering successful treatment to the patient from whom the cells have been isolated. For allogeneic cells, broad detection assays are also used to address the risk of ‘unknown’ and known contaminants being passed from donor to recipient. Tests include the use of transmission electron microscopy, NGS, and in-vitro cell-based assays,” he says.

COMMERCIAL SCALE
For commercial-scale manufacturing in the case of allogeneic cell therapies, it is important to perform cell banking and cell characterization to support scale up. This includes establishing and testing the working cell bank (WCB) and cells at the limit of in-vitro cell age (LIVCA) separate from the original master cell bank (MCB).

Bulpin points out that the specific requirements for the detection of contaminants at the WCB and LIVCA level are laid out in relevant regulations and guidelines for advanced therapy medicinal products (ATMPs). These requirements are similar to the requirements for the MCB, with less testing required at the WCB level. “In particular, the risk of introducing contaminants during scale-up must be addressed through testing, including the detection of human viruses, bacteria, fungi, mycoplasma, and pyrogens,” he says.

The requirements are similar for controlling the vector material and associated production cells. Rigorous testing should be performed on all starting and in-process materials, such as plasmids, vector production cell banks, vector bulk harvests, and purified bulk, says Bulpin. It is at this stage that specific risks, such as the presence of replication-competent viral vectors in bulk harvest and transduced cells must be addressed, he explains.

CELL PURITY VALIDATION
When moving from clinical to commercial-scale manufacturing for a cell therapy, other considerations must be taken into account, and phase-appropriate validations used to assess the materials. During early clinical phases, for example, assays used for the release of clinical material should be suitably validated and qualified in the presence of a test matrix that uses a single batch of material. For late-stage or commercial-scale development, assays should be fully validated and qualified in the presence of a test matrix using a minimum of three batches under a formal product-specific qualification, Bulpin says.

A battery of tests is generally used to assess and validate the purity of the cell therapy end-product. Tests include PCR assays for viral pathogens and mycoplasma and a sterility assay for bacteria and fungi. For cell therapies that have been transduced using a viral vector, the risk of replication-competent virus being present must be addressed, Bulpin asserts. This is typically done using a detector cell-based in-vitro cultivation assay with a vector-specific endpoint test. “Furthermore, purity of the cell therapy must be authenticated to the level of the individual. Finally, assays used for lot release of clinical or commercial material should be suitably validated and qualified in the presence of a test matrix,” he concludes.

ADVANCED ASSAYS
The complex nature of cells and cell-to-cell interactions calls for advanced assays to help detect even minute levels of contamination and to validate their purity. The most advanced analytical assays that are used for detecting contamination in human cell sources include novel molecular sensitive techniques with broad molecular detection capabilities. Examples include deep sequencing/next-generation sequencing/high-throughput sequencing, degenerate polymerase chain reaction for whole virus families or random priming methods, hybridization to oligonucleotide arrays, and mass spectrometry, according to Bulpin.

REFERENCES
Biosimilars Tackle Interchangeability Standards

Demonstrating interchangeability can ensure biosimilar substitutability at the pharmacy level.

FELIZA MIRASOL

In May 2019, FDA published a final guidance (1) on demonstrating biosimilar interchangeability and recommended what analytical assessments and data should be included for a biosimilar to qualify as a substitution for a prescribed originator biologic. Unlike the generic versions of small-molecule innovator drugs, biosimilars cannot simply be substituted for branded biologics.

VARIABILITY PLAYS A ROLE

A generic version of a small-molecule drug has to be shown as being chemically identical to its predecessor, but the term “identical” cannot be used in discussion about biologics for the simple reason that there is variability among lots in all biologics, including reference products, notes SangJoon Lee, senior executive vice-president at Celltrion. “These inherent variabilities are based on factors such as heterogeneous protein production from a living organism cell line and changes in manufacturing processes. The extent of variations in different lots of the original biologic should be measured by biosimilar companies to regard these variations as acceptable boundaries for a biosimilar,” says Lee.

Because biosimilars, unlike small-molecule drugs, are manufactured in living cell lines using processes that cannot be exactly replicated from one manufacturer to the next, biosimilar manufacturers must demonstrate that the biosimilar is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product in terms of safety and effectiveness, adds Leah Christl, executive director, Global Regulatory and R&D Policy, Amgen.

“An additional showing is needed to support an interchangeability determination,” Christl continues, “If FDA determines that a biosimilar meets the interchangeability standard, that biosimilar may be substituted at the pharmacy under state pharmacy laws.”

“What makes the US biosimilar market different from other highly regulated markets, such as Europe, Canada, Japan, or Australia, is that the regulatory pathway in the United States includes a determination of ‘interchangeability’ between the reference product and biosimilar—a designation that permits pharmacists to substitute a biosimilar for its reference medicine without needing to first obtain permission from the prescribing physician. Without this designation,
Event Overview

Biotherapeutics such as monoclonal antibodies (mAbs) are frequently glycosylated, and the structure of attached N-glycans can affect immunogenicity, pharmacokinetics and pharmacodynamics. This can make glycosylation a critical quality attribute (CQA), making characterization of N-glycans an essential part of the development process. We present complete N-glycan quantitation workflow solutions using liquid chromatography (LC) with fluorescence detection (FLD) or mass spectrometry (MS) for four levels of biotherapeutic analysis: intact mass, mAb subunits, glycopeptides, and released glycans. Released N-glycans are labeled with InstantPC (a glycan dye that provides high FLD and MS signal) or 2-AB (a traditionally-used label) prior to separation by hydrophilic interaction liquid chromatography (UHPLC-HILIC). Sialylation of biotherapeutics can also be important, and we present a plate-based streamlined workflow for quantitation of total sialic acid.

- Relative quantitation of mAb glycoforms at intact protein and mAb subunit level using the highly sensitive LC/Q-TOF system
- Use of HILIC column for glycopeptide separation and quantitative analysis by LC/MS
- Rapid and reproducible sample preparation for released N-glycans (1 hour for InstantPC, 2 hours for 2-AB)
- Analysis of InstantPC labeled mAb and Fc fusion protein N-glycans, including relative quantitation by LC/FLD and glycan structure assignment by LC/MS
- Quantitation of total sialic acid using a plate-based colorimetric assay with a broad range of detection

Key Learning Objectives

- Importance of N-glycan analysis for biotherapeutic proteins
- Multi-level LC/FLD/MS approaches to quantitate N-glycans and sialic acid content of biotherapeutics
- Choosing a fluorescent dye and analytical separation method for released N-glycans

Who Should Attend

- Biopharmaceutical analytical development scientists

For questions or concerns, email mdevia@mmhgroup.com.

Multi-Level Workflows for Quantitative N-Glycan and Sialic Acid Analysis of Biotherapeutics

LIVE WEBCAST:
Europe & US Broadcast: Tuesday, March 31, 2020 at 9am EDT | 2pm BST | 3pm CEST
US Broadcast: Tuesday, March 31, 2020 at 2pm EDT | 1pm CDT | 11am PDT
Asia Pacific: Wednesday, April 1, 2020 at 8:30am IST | 12pm JST | 2pm AEDT

Register for this free webcast at: http://www.chromatographyonline.com/lcgc_p/biotherapeutics

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BioPharm
pharmacists first need to contact and obtain permission from the prescribing physician before they substitute a biosimilar for an originator biologic,” says Hillel P. Cohen, PhD, executive director, Scientific Affairs, Sandoz, a Novartis company.

An FDA-approved biosimilar does not necessarily need an interchangeability designation to be approved for all indications of the originator biologic, however, notes Noelle Sunstrom, founder and CEO of NeuClone, an Australian-based clinical-stage bio-pharmaceutical company. “For example, while none of the five Herceptin (trastuzumab) biosimilars approved by FDA are designated as ‘interchangeable,’ they all are approved for the same indications as the originator. Interchangeability only relates to the practice of a pharmacist substituting a biosimilar for an originator biologic,” Sunstrom emphasizes.

“A major reason a biosimilar is not ‘simply’ designated to be substituted, in the same way as a small-molecule generic, relates to the variable structure of biologic medicines, which can affect their potency and blood half-life in patients,” Sunstrom says. “For small molecules drugs, the precise atomic structure of the originator product is well defined and expected not to change. Thus, following patent expiry of the originator small-molecule drug, another manufacturer can manufacture a generic alternative that is an exact replica of the originator, and can be highly controlled down to the atomic level.”

“However, with biologics, such precise replication cannot be achieved because all biologics—whether an originator or a biosimilar—vary from one batch to the next. This inherent variation is the result of using living cells used to manufacture biologics that are heterogeneous mixtures of different molecules with different post-translational modifications (PTMs). So, biosimilars can be ‘highly similar’ to an originator biologic that itself exhibits batch-to-batch variability,” Sunstrom clarifies.

Variations in PTMs of a protein, including the molecule’s glycosylation profile and formation of disulphides, are cell line dependent, says Matt McGann, field applications and marketing manager at RedShiftBio, a Burlington, MA-based provider of analytical instrumentation.

“Many innovator pharmaceutical companies have gone to great lengths to develop unique cell lines for production of a biotherapeutic product, thereby limiting the ability to simply copy a drug substance,” McGann says.

“The processes involved in developing a biosimilar result in variations in the protein from primary to quaternary structure,” McGann continues. “The new FDA guidelines for interchangeability of a biosimilar highlight these differences by recommending that biosimilarity not only be established based on pharmacological attributes of the drug substance but also clinical data, such as clinical end-points and interchangeability. Demonstration of an equal or better patient outcome is considered required evidence to justify the licensing of a bio-similar drug, which is described at the totality of evidence by FDA.”

CLARIFYING INTERCHANGEABILITY
For practical purposes, clarifying what “interchangeability” means is helpful in biosimilar development. “Interchangeable” means “biosimilar plus,” where the product must first meet the requisite hurdles to qualify as a biosimilar, notes Jennifer Mallory, partner at Nelson Mullins Riley & Scarborough, a Columbia, SC-based law firm. Following this, the biosimilar manufacturer must meet heightened evaluation and testing requirements.

“These are designed to ensure that the biosimilar produces the same clinical result as the approved biologic in any patient and that the safety and efficacy risks arising from switching between the approved biologic and the biosimilar are not greater than the risk of using just the approved biologic,” Mallory says.

The additional hurdles are designed to ensure that a biosimilar may be substituted for the reference biologic without the need for intervention by the health care provider who prescribed the original reference biologic, Mallory adds.

As part of FDA’s standard, a manufacturer of a proposed interchangeable biosimilar product must show the product is highly similar to, and has no clinically meaningful differences from, its reference product, states Christl. Christl also points out that biosimilarity is not equivalent to interchangeability. The latter is intended to support automatic pharmacy-level substitution and needs to be positively established on a case-by-case basis, Christl also says.

“It is important to note that a biosimilar without an interchangeability designation is not inferior to a biosimilar with the designation,” Christl points out. “Instead, an interchangeability designation reflects a determination by FDA that the biosimilar can be substituted for the reference product at the pharmacy without the consent of the prescriber. This determination is based, in part, on additional data showing that patients can be switched back and forth between the reference product and the biosimilar with no additional risk.”

Based on its own internal analyses, Amgen believes that only about 10% of biological products (excluding insulin and human growth hormone) are expected to lose regulatory exclusivity by 2023 in the US. These products are dispensed at retail pharmacies where automatic substitution could occur, Christl notes. “We are seeing many biosimilars contribute to competition and attain strong uptake in the US, even though FDA has not yet designated any biosimilar as interchangeable.”

Christl also states that FDA’s interchangeability guidance does not substantively address analytical testing or...
analytical standards beyond what the agency already has addressed in earlier guidance on the demonstration of biosimilarity. “In terms of clinical testing, FDA’s interchangeability guidance states that sponsors seeking an interchangeability designation for a product intended to be used more than once by an individual are generally expected to conduct switching studies, in which patients start with the originator product and are randomly assigned to switch to the biosimilar or continue using the originator product. According to the guidance, the ‘switching’ group would be expected to incorporate at least two switches between the originator and biosimilar products and at least two exposures to each product,” says Christl.

“Amgen believes that FDA’s current standards for demonstrating interchangeability are scientifically appropriate,” she adds.

“It is quite important for a biosimilar to demonstrate ‘interchangeability’ because, unlike generics, a biosimilar can be prescribed by physicians under the current law. Despite biosimilar use over the years, there has been a hesitation to prescribe them because of potential risks, such as diminished efficacy or expectation of immunogenicity after switching to a biosimilar,” says Lee. Lee notes, however, that the designation of interchangeability based on efficacy results from multiple switching will encourage physicians and patients to use biosimilars more often. Furthermore, interchangeability status ultimately allows for any product among available interchangeable products to be dispensed at pharmacy level, which is expected to accelerate access to biosimilars.

The interchangeable designation in the US requires additional clinical data beyond that provided to establish biosimilarity, Cohen points out. “It is not a higher quality standard because an interchangeable biologic and biosimilar, by definition, match the reference product in safety, purity, potency, and efficacy.

**IS INTERCHANGEABILITY STATUS IMPORTANT?**

The importance of interchangeability is particularly relevant for biologics dispensed by pharmacists for patients with chronic illnesses because these patients require treatment over a long period of time, notes Sunstrom.

However, Sunstrom explains, if a treatment is only for a short duration, such as with many oncology biologics, the patient can receive fewer doses, thereby reducing the opportunity for switching between an originator and biosimilar. If the prescriber is also administering the biologic (i.e., no decision by the pharmacist), the prescriber has total control over whether an originator or biosimilar is administered with no opportunity for pharmacy-level substitution, making an interchangeability status in cases such as these less significant.

“Note that, as of March 12, 2020, none of the 26 FDA-approved biosimilars have been designated as interchangeable,” Sunstrom observes.

Further, there has been debate over the need for an FDA interchangeability designation at all. “Interchangeability is an additional attribute to a biosimilar that comes at a substantial investment in clinical trial design, which incorporates switching originator with biosimilar and back again in large-patient-number trials. It does not designate the interchangeable biosimilar as being superior in any way to those without this designation,” Sunstrom states.

Cohen holds a similar opinion, saying that, as a scientific matter, a biosimilar is developed to match its reference medicine with regard to these attributes. “Therefore, it is our position that an approved biosimilar should be considered interchangeable with its reference medicine, meaning that a patient can expect an equivalent treatment outcome,” Cohen adds.

“To date, there are 26 FDA-approved biosimilars, but only 16 are marketed in the US [as of press time]. In comparison, the European Medicines Agency (EMA) has approved 64 biosimilars, 59 of which are available for use in Europe. While we are encouraged that healthcare systems in the US are implementing biosimilars into their clinical practices at a growing rate, there are still hurdles that need to be addressed to support a biosimilar market that can generate success like what we’ve seen in Europe,” states Cohen.

One hurdle includes the challenges posed by FDA’s approval process for interchangeability, specifically, the fact that to obtain interchangeability, sponsors are required to conduct an extensive, comparative pharmacokinetic (PK) study using multiple switches followed by an extended follow-up period. “This criterion is not mandated for PK studies of originator biological drugs when manufacturing process changes are implemented that lead to structural changes of the biological drug itself. The additional research burden and costs for a biosimilar drug to be considered interchangeable are substantial and may deter biosimilar manufacturers from seeking interchangeability,” Cohen emphasizes.

The value of the interchangeable attribute, therefore, is in the automatic substitution at the pharmacy level. “In Europe, there is no equivalent designation from the European Medicines Agency (EMA) and switching between originators and biosimilars is a medical matter typically at the discretion of the prescribing physician, not the pharmacist. As argued by Ebbers & Schellekens (2019), biosimilars should be interchangeable by default rather than needing to meet additional requirements to be designated as such: ‘there is no reason to doubt that biosimilars are interchangeable and that the risk of increased immunogenicity of switching to a biosimilar is no greater than switching between two batches of any biologic. We argue that the default should be that biosimilars are inter-
changeable, unless there is compelling evidence otherwise." Sunstrom cites (2).

**ANALYTICAL GUIDANCE**

When it comes to analytical recommendations in the FDA interchangeability guidance, a key phrase to take note of in Section V.A.1: "Advances in analytics may allow for extended analytical characterization that affect the extent of other data and information needed to support a demonstration of interchangeability..." (1).

McGann points out that this statement highlights the fact that improvements in analytical methods for characterizing biotherapeutics can drastically impact the totality of evidence required to support the claims of biosimilarity. "Improvements in instrumentation capabilities, such as sensitivity, resolution, or precision that can more clearly demonstrate biological similarity could reduce the burden of proof required to demonstrate both biosimilarity and interchangeability," McGann says.

Advanced analytical tools (e.g., AQS3pro, RedShiftBio) can offer a 30x improvement in sensitivity and the ability to measure secondary structure in formulation conditions. The latter measurement was not previously possible, and it could provide evidence of biosimilarity that reduces the burden of proof in other areas, McGann says.

"For this reason, biosimilar developers need to ensure that their analytical tools are at the cutting edge of technology. As a company, they need to be constantly reviewing their capabilities to ensure that they stay at the forefront of technology relative to the market," McGann adds.

"FDA, in recent years, has taken less of a prescriptive stance when it comes to what types of analytical characterization should be used, preferring to move the responsibility to the pharmaceutical company to justify why a measurement is not required rather than requesting specific tests to be performed. This change can be attributed to the rapid change in technology in recent years," explains McGann.

Celltrion backs up that perspective. Lee says that, instead of providing any specific analytical recommendations that biosimilar developers can implement, the new guidance explains the agency’s position, which discusses the planned development approach. This approach includes any proposed justification for reducing the extent of information needed to support a demonstration of interchangeability by the extended analytical characterization. "Our company is planning to discuss reasonable approaches for each product with the regulatory authority to reduce the burden of clinical trials," Lee states.

What the guidance does provide are examples that sponsors may employ as benchmarks to assess the approaches they are thinking of using to demonstrate interchangeability and to develop their product development plan, says Mallory. Mallory also notes that it is advisable to identify the approaches highlighted in the guidance document that a sponsor already used in its development work and previously submitted to FDA in connection with the biosimilar approval process. "Likewise, sponsors would be well-served to determine which approaches in the guidance document do not appear applicable (and why), and any short cuts that potentially may be available. Some of this analysis ideally would take place even before early discussions with FDA so that the sponsor can be comfortable with the specific goals and objectives that it would like FDA to green-light or begin to consider," she highlights.

An important theme in the guidance, Mallory emphasizes, is that FDA is not suggesting that there is a one-size-fits-all approach for demonstrating interchangeability. Rather, the agency used the guidance to confirm that demonstrating interchangeability is complex, much like the complex molecules involved. "Thus, FDA noted in the guidance that the ‘data and information necessary to support a demonstration of interchangeability need to be considered on a case-by-case basis,’" Mallory says.

Given FDA’s perspective, it is therefore helpful that the guidance repeatedly emphasizes that sponsors are encouraged to reach out to the agency to conduct early discussions and schedule meetings. "Additionally, as stated in the *Federal Register* notice regarding the guidance, FDA is not suggesting that this will be its final word on interchangeability. Indeed, in February 2020, FDA issued additional draft guidance, entitled *Biosimilars and Interchangeable Biosimilars: Licensure for Fewer than All Conditions of Use for Which the Reference Product Has been Licensed* (3). We can expect upcoming agency guidance and other actions that hopefully will provide more insight for developers of biosimilars and interchangeable biosimilars," Mallory concludes.

"The analytical processes and tools used in biosimilar development are very similar to those used in the development of originator biological products. The primary difference is how those tools are used in the iterative process of biosimilar development. While the methods and tools are technically complex (thus, not simple), they can be utilized in a fairly straightforward manner to develop biosimilars that meet the criteria of 'highly similar with no clinically meaningful differences',' Christl adds.

**REFERENCES**


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Being Vigilant in Supplier Oversight

Risk assessments, audits, and good communication between sponsor and supplier are key elements of supplier oversight.

SUSAN Haigney

The bio/pharmaceutical industry is a global network that ties together an array of developers, manufacturers, and suppliers. Bio/pharmaceutical companies, therefore, may source APIs and excipients from companies thousands of miles away. This global aspect of the industry, naturally, creates a complex supply chain that could leave patients vulnerable if not properly overseen. The discovery of nitrosamine impurities, including N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA), found in angiotensin II receptor blocker (ARB) medicines (1) in 2018 is an example of how ingredient issues can affect patients and the supply chain and the importance of testing ingredients. Now, the global COVID-19 coronavirus pandemic has the potential to disrupt supply chains, site inspections, and other activities associated with supplier qualification and oversight.

Sponsor companies and manufacturers are responsible for ensuring the components they use are safe and effective. FDA has cited companies for failing to test their incoming API and raw materials “to determine their identity, purity, strength, and other appropriate quality attributes” (2). According to a spokesperson for IPEC-Americas, sponsor companies must verify the quality of materials, which includes qualification of the supplier through on-site good manufacturing practice (GMP) audits and/or a third-party GMP certification. Incoming materials should have their identification verified and the quality department should give its approval to release the materials for use. This includes performing—at a minimum—an identification test, and may include other tests necessary to ensure the quality for the intended use as per 21 Code of Federal Regulations 211.84(d)), advises IPEC-Americas.

Risk assessments of both suppliers and materials should also be performed, according to IPEC-Americas, with a specific focus on the intended use of the material. The risk assessment should also evaluate possible concerns with efficacy, variability, safety, and quality. And this evaluation should not end with the risk assessment. The sponsor should “[establish] a process for continued monitoring of the supplier and the quality of incoming materials,” according to IPEC-Americas.

QUALIFYING SUPPLIERS

How do sponsor companies choose and monitor material suppliers to ensure the ingredients they are purchasing are fit for purpose? Linda Evans O’Connor, vice president and chief of staff at Lachman Consultant Services, Inc., suggests that sponsors start by obtaining information from the supplier about its capabilities and compliance history through a questionnaire. Material
BioPharm International spoke with Jens Andersson, purchasing director at Cambrex Karlskoga, about the best way to ensure the security of the bio/pharmaceutical materials supply chain.

BioPharm: What is the contract manufacturing organization’s (CMOs) responsibility in ensuring the quality of materials they use in the production of APIs?

Andersson (Cambrex Karlskoga): Cambrex prefers to take full responsibility for ensuring the quality of the raw materials that are used in our manufacturing processes. Ultimately, we are responsible for the quality of the final API produced at our sites and ensuring that it meets customers’ specifications. Therefore in our opinion, it makes sense that we take the responsibility to source raw materials of the correct quality to undertake the campaign or product. We also find this process to be quicker and more cost-effective than if the end customer undertakes the sourcing and sends material to us, as we can use our own supplier network and can use suppliers with which we have a well-established relationship without having to necessarily qualify new suppliers.

BioPharm: What are the steps and/or best practices for qualifying suppliers?

Andersson (Cambrex Karlskoga): There are several steps that are undertaken when we qualify suppliers, with the first being to evaluate the quality of raw materials against the specifications to ensure that they meet both the stated purity and the demands of the project we intend to use the materials for. Then we send questionnaires to the suppliers that cover a wide range of topics, from quality to health and safety practices, as well as environmental policies and responsibilities, and ethical guidance of the company. If needed, audits are carried out on-site by our QA [quality assurance] specialists for suppliers of raw materials with critical impact on the final product quality, such as the main building blocks of the final API.

BioPharm: How often should suppliers be audited?

Andersson (Cambrex Karlskoga): For critical raw materials and services we re-evaluate suppliers every two years. We carry out on-site audits every two to three years depending on how critical the raw material or service is; however, audits can also be initiated outside of the regular schedule for other reasons, such as quality or supply issues.

BioPharm: What additional challenges do high-risk materials pose? Does the oversight of these suppliers intensify?

Andersson (Cambrex Karlskoga): The main challenge is that for suppliers of critical raw materials we need to make a much more thorough initial qualification and risk assessment. This can be time consuming and, at times, it can be difficult to get the data and information needed. At Cambrex, we do have a robust supplier network where we have been able to establish strong relationships over a number of years that mitigates this risk.

BioPharm: When there have been reports of suppliers falsifying certificates of analysis (CoAs), how can a pharma company or contractor be sure the information they are receiving from a supplier is correct? Is this why testing of materials is important?

Andersson (Cambrex Karlskoga): For critical raw materials, we will always carry out our own analyses to confirm the vendor’s CoA and ensure the quality of the material. For less critical raw materials such as common solvents or regularly used bulk acids and alkalis from reliable and trustworthy vendors, goods can be received only on CoA, but we will undertake random tests to ensure the CoAs.

BioPharm: What should a pharma company or contractor do when FDA puts a supplier on import ban? Should companies have a backup plan to prevent product shortages?

Andersson (Cambrex Karlskoga): A company needs to be proactive and should always aim for dual sourcing capabilities for critical raw materials, so that any risk of supply is minimized. A risk assessment should always be carried out to evaluate the danger of interrupted deliveries.

BioPharm: What has the recent N-Nitrosodimethylamine (NDMA) impurity issue taught the industry about materials quality and the importance of testing materials?

Andersson (Cambrex Karlskoga): Given that the situation with the NDMA is still ongoing, it is too early to say what lessons need to be learned from it. However, in 6–12 months the situation will hopefully be clearer, allowing for a detailed review to take place and evaluation of any future risks to be made. It is paramount that patient safety is the highest priority so the industry as a whole has a duty to ensure that decisions are made that do not compromise this in any way, and that any oversights that have been made previously do not happen again.

—Susan Haigney
samples should also be obtained to determine if they are fit for their intended purpose. Site audits should be performed, and quality agreements should be put in place, she says. Finished product trials should be performed if the materials meet the requirements. Batches should then be tested for stability. Periodic monitoring of the supplier should be performed with data reviewed on a predefined basis in addition to performing surveillance audits, according to O’Connor. IPEC-Americas stresses, however, that an appropriate risk assessment cannot be performed without onsite audit information.

Susan J. Schniepp, executive vice-president of post-approval pharma and distinguished fellow, Regulatory Compliance Associates, says that companies should begin the qualification with an onsite audit. “Once the audit is performed and any identified concerns resolved, the two parties, purchaser and supplier, can enter into a quality agreement. After the quality agreement is approved, the purchasing company can start the process of qualifying the supplier. This qualification usually involves testing of the material to confirm the supplier’s certificate of analysis (CoA) is accurate and develop a history that demonstrates the ability of the supplier to continually provide a suitable product,” says Schniepp.

The supplier should then be placed on an approved supplier list, according to Schniepp. “The initial qualification for a supplier to be considered an approved supplier usually involves complete confirmatory testing on the first 10 lots of material received and then a periodic check and confirmation by the purchaser of the entire testing regimen listed on the CoA received from the supplier.”

PERFORMING AUDITS

Performing audits of material suppliers is key for ensuring the quality of materials, but how often should these audits be performed? O’Connor suggests that a risk-based approach should be used to determine when and how often a supplier is audited. “Many factors can go into the risk model, such as type of material (e.g., API, excipient, sterile, non-sterile, complex dosage form, etc.), location, past regulatory or audit history, recalls, quality of incoming goods, complaint history, importance to the business of the materials (i.e., Is this an API for your blockbuster drug and lack of supply would have a material impact on the business?). A minimum frequency per material type should be defined (i.e., for an API, every two years),” O’Connor says.

IPEC-Americas agrees. “Whether the supplier is an excipient manufacturer, contract manufacturer, distributor, or service provider (e.g., a contract testing lab), the initial audit frequency should be based on results from the initial supplier/excipient risk assessment along with any additional mitigation measures identified. Based on on-going monitoring, a sponsor company should determine whether to adjust the audit frequency.”

A quality risk management plan is key, agrees Schniepp. Frequency of audits should be based on the criticality of the material and the past performance of the supplier. “This plan should identify supplier vulnerability (i.e., single source, secondary supplier, etc.), which should help determine audit frequency. The quality agreement should reflect the risk plan, but there should always be a contingency to allow for-cause audits as needed. Laboratories used by either the supplier or the purchaser should be audited and included as an element of the risk plan,” says Schniepp.

Auditing under difficult circumstances

Having a consistent and properly executed audit program is paramount to maintaining the timeliness and integrity of the supply chain, says Schniepp. Audits, and the information obtained during them, allow one to assess a supplier’s risk, especially during crises such as the COVID-19 pandemic. “Having the baseline knowledge of your suppliers’ operations will help assess where critical resources need to be allocated during a crisis period. While not ideal, audits can still be performed on suppliers through the use of questionnaires and video conferencing. If visuals are required for the supplier assessment, the use of an electronic device or video streaming options could be employed. Bottom line, to keep the supply chain viable during crisis mode, we need to think outside of our normal operating procedures and experiences,” says Schniepp.

If travel is limited due to global situations such as the COVID-19 epidemic, O’Connor suggests getting creative. “For example, performing a virtual audit, while not ideal, is a possibility, and would require cooperation of the sponsor and the manufacturer. Document review and interviews can be performed remotely. Companies could even look at virtual facility tours using appropriate technology. However, these types of audits are not ideal, and shouldn’t replace on-site audits. Another solution is to partner with a local company that has the local resources to perform the on-site portion of the audit. This will allow on-site audits to occur even when international travel bans are in effect,” says O’Connor.

THE ROLE OF COAs

CoAs provide manufacturers with detailed information about materials including material manufacturer, quality testing information, specifications, batch numbers, and other information (3). FDA has been known to cite companies for incomplete or incorrect information on CoAs (4). So, how reliable are these documents and how much emphasis should sponsors put on them when it comes to ensuring material quality?

O’Connor suggests that sponsor companies create a library of CoAs or labels so they can verify that the information is correct. “Also, maintaining a relationship with suppliers is key. Anything unusual needs to be flagged,” says O’Connor.

Building trust between the sponsor and supplier is important, agrees IPEC-Americas. “A robust supplier qualification program, including an onsite GMP assessment of a supplier, by either the sponsor or a qualified third party, and development of a partnership with
the excipient supplier are necessary to establish and build trust in the validity of their CoA,” says IPEC-Americas.

Annual confirmation testing of CoA results is also necessary, says IPEC-Americas (5). “Full testing of an excipient is required until a robust supplier study has been completed and a reduced testing program has been approved. Only once trust has been established can the sponsor move to a reduced testing program. However, identification testing is always required to ensure the identity of incoming materials.”

To establish that the quality testing information included in the CoA is accurate, incoming materials must be tested against the requirements in the CoA, Schniepp insists. “The best way to ensure the CoA is accurate is through complete testing. In cases of falsification of the CoA, results testing is mandatory to make sure the material is suitable for use; however, it must be coupled with a review of the supplier’s overall quality system. Even if the material meets the testing qualifications listed on the CoA, it may not be suitable for use due to other potential GMP violations that might be present at the supplier facility,” she says.

“In the case of falsification, the purchaser should be concerned with data integrity issues that lead to the falsification in the first place. If a purchaser suspects a supplier is falsifying the results on a CoA they need to initiate a for-cause audit and quarantine the suspect material until they can confirm it was satisfactorily manufactured following cGMP expectations. Passing test results does not confirm compliance to cGMPs,” Schniepp explains.

**THE ROLE OF CMOs**

Many drug sponsors engage contract manufacturing organizations (CMOs) to conduct drug production steps. So what is the CMO’s responsibility in ensuring that materials are safe and effective?

O’Connor says that while both sponsors and CMOs share responsibilities, the sponsor has the “ultimate” responsibility of its supply chain. “Sponsors and CMOs share responsibilities, but the selection, qualification, and oversight of suppliers is the sponsor’s responsibility, whereas day-to-day testing is generally the CMOs/CDMOs, although sometimes that goes to the sponsor as well. The sponsor has ultimate responsibility for the entire supply chain, so even if it delegates part of that responsibility to the CMO/CDMO, it is ultimately responsible.”

Sponsors must ensure that they have signed agreements in place with any CMOs and/or CDMOs they are using that identifies the responsibilities of each party when it comes to ensure the quality of materials, according to a spokesperson for IPEC-Americas.

*Contin. on page 56*
Packaging Preserves the Cold Chain

More sustainable and functional cold-chain packaging protects temperature-sensitive drugs.

Proper storage and transport temperatures for drugs, especially biologics, are essential to protect product efficacy and patient safety. “As strong growth continues across the global pharmaceutical industry, the sub-category of temperature-controlled products is surging ahead—growing at twice the rate of the industry overall,” said David Williams, president of Pelican BioThermal in a press release (1).

Joe Cintavey, product specialist at W.L. Gore, agrees, noting, “The pipeline of biologic drugs in development are becoming more temperature-sensitive, resulting in an increase in storage of bulk drug substance at frozen temperatures (-40 to -70 °C).”

Rory Davidson, Business Development Manager at Almac Pharma Services, adds that labeling, packing, and distributing cell and gene therapy products often requires products to be stored and processed at ultra-low temperatures (-20 to -80 °C), with the products only being defrosted immediately prior to use. “If these products are not kept in exact conditions, they become unusable. We have seen some cases of product becoming unusable within a minute of being out of frozen conditions and so we need to be able to handle and process product at these ultra-low temperatures as quickly and efficiently as possible,” notes Davidson.

PACKAGING TRENDS

In addition to the growing number of temperature-sensitive products, three trends are driving the need for temperature-controlled packaging, according to a survey by Pelican BioThermal. First, quality demands increase as more sensitive products bring logistics complexity and greatly expanded risk. Yet, while awareness of temperature-controlled requirements is high, the survey shows temperature excursions happen frequently (1).

Second, the distribution range is expanding as products move further and through more climatic zones. More than half of survey respondents (51.8%) regularly ship products internationally, creating an increasingly complex web of local, regional, and international connections that require a broad range of transport modes (1).

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Understanding Oligonucleotides from Every Angle: Utilizing Mass Spectrometry for Characterization and Quantification

ON-DEMAND WEBCAST: Aired Tuesday, March 17, 2020

Register for this free webcast at: http://www.chromatographyonline.com/lcgc_p/angle

Event Overview
Therapeutic oligonucleotides continue to grow in their contribution to the pipelines of pharma and biopharma companies. Oligonucleotides are a chemically distinct class from small-molecule or protein therapeutics and present their own unique challenges for characterization and quantification. As a consequence of their highly serial synthesis and use of modified nucleotides, oligonucleotides are uniquely susceptible to fairly high levels of synthetic impurities.

Quantification of oligonucleotides is complicated by the typical use of ion-pairing reagents. A simple way to overcome this is to use a lower flow that maintains system uptime and increases sensitivity. In addition, this webcast will provide details on the advances of current techniques for microflow LC-MS quantification of oligonucleotides.

Key Learning Objectives
- Gain a broad understanding of the different classes of therapeutic oligonucleotides currently in development
- Discover how microflow LC-MS allows us to get the highest sensitivity of oligonucleotides in complex biomatrices
- Learn how high-resolution mass spectrometry (HRMS) allows you to get definitive confirmation of oligonucleotides’ synthetic impurities

Who Should Attend
- Scientists or lab directors already supporting oligonucleotide therapeutic development or those considering doing so

For questions or concerns, email mdevia@mmhgroup.com
There is strong demand for more sustainable designs, including re-use programs to reduce the carbon footprint.

In addition to insulation, temperature-controlled packaging includes single-use and reusable parcel and pallet shippers, thermal pallet covers, and phase-change materials. Sometimes, customized designs are needed, especially for products that will experience particularly hostile conditions or need to be maintained at cryogenic temperatures. Regardless of the application, optimized temperature-controlled packaging depends on the answers to three questions: Where is it being shipped? What temperature must be maintained? How long does that temperature need to be maintained?

In addition, “Seasonal temperature changes can substantially affect the internal facility environment and shipping environment,” warns Joe Luke, vice president of sales and marketing for Reed-Lane, a New Jersey-based provider of contract packaging services.

**TESTING**

To ensure packaging will perform as specified, Cryopak tests it against extreme ambient temperature profiles in its ISTA-certified lab following protocols and internal standard operating procedures. “Our shipping systems are then qualified with repetitive testing to assure consistency and performance repeatability,” explains Barakat. “The real shipment is then monitored with temperature data loggers to prove operational performance and quality assurance,” he concludes.

To test the durability of reusable, passive thermal packaging systems, Pelican BioThermal is developing a mechanical test method. In addition to mimicking the real-world use environment, the test method also allows assessment of the impact of dynamic use on thermal performance. Tetz reports that results are promising. He says, “The test standard would give pharmaceutical manufacturers even more confidence in choosing reusable thermal packaging over single-use options to reduce costs and advance environmental initiatives.”

“Current standards assess parcel thermal packaging during one intense shipment from point A to point B,” explained Bill Mayer, director of research and development at Pelican BioThermal. “Throughout the development of this new test method, we addressed the challenges of exposing systems to the multi-leg and multi-mode shipping route and more of an average trip with parcel thermal packaging used multiple times” (2).

**COLD-CHAIN OPTIONS**

Innovations in temperature-controlled packaging center on sustainability, performance, and cost. To

The third trend identified in the survey is the need to optimize the total cost of ownership (TCO) due to relentless competition and margin pressures. A full 70% of survey respondents agree that TCO is “important” or “very important,” while 10% consider only basic packaging costs and transport rates. This exploration of TCO is spurring interest in reusable containers, with 79% of survey respondents saying reusable containers—though more expensive than single-use containers—are worth the investment. More than one-third of respondents (37.6%) are already using reusable rental programs in their cold-chain logistics operations, and 25% are actively exploring this option (1).

As a result, validated, off-the-shelf, or customized protective packaging options continue to evolve for all temperature ranges, including controlled room temperature, refrigerated, frozen, and cryogenic. “The challenge is optimizing the design, materials, and components to minimize overall size and weight of the shipping solutions,” says Mark Barakat, general manager of Cryopak, a subsidiary of Integreon (formerly TCP Reliable). He continues, “Achieving peak performance while minimizing size, weight, and cost is typically contradictive.” Cold-chain engineering experience and tools like thermal modeling software and testing equipment play important roles in optimizing temperature-controlled packaging.

**MEETING REQUIREMENTS**

There is also strong demand for more sustainable designs, including re-use programs to reduce the carbon footprint. Interest in temperature-controlled packaging also is being impacted by changing regulations and standards. For example, “Temperature profiles issued by ISTA [International Safe Transit Association] have changed within the past five years,” reports Barakat.

“Regulations governing these types of highly sensitive products are growing stricter,” adds Adam Tetz, director of worldwide marketing at Pelican BioThermal. “For example,” he says, “China has become particularly strict and requires real-time tracking on all pharmaceutical shipments.”

Many local governments want to reduce or eliminate the use of expanded polystyrene foam (EPS), a common insulating material, because it is rarely recycled. “California and New York are limiting the amount of EPS foam that can be delivered into their states,” says M. Ryan Corbin, director of marketing at Kodiakooler. These requirements are forcing makers of temperature-sensitive drugs and biologics to look for alternatives.
Simple and Effective Methods for Purification and Determination of Molecular Weight of DMT-on and DMT-off Oligonucleotides

Event Overview
The pipeline of oligonucleotide drugs has never been stronger. This has created the need for innovative purification and analytical characterization techniques. In this presentation, new simple, fast, and effective methods for the purification—as well as the molecular weight analysis—of DMT-on oligonucleotides and DMT-off oligonucleotide therapeutics are discussed, including:

• Purification of a protected or DMT-on oligonucleotide using hydrophobic interaction chromatography (HIC)
• Purification of a charged-oligonucleotide using anion exchange chromatography (AEX)
• Use of a fast and effective analytical method to determine the molecular weight of oligonucleotides by HPLC size-exclusion chromatography (SEC) coupled with light scattering detection

Key Learning Objectives
• Understand purification methods recommended for purifying a protected or DMT-on oligonucleotide
• Learn purification methods recommended for purifying a charged-oligonucleotide
• Understand why size-exclusion chromatography coupled with light scattering detection is considered an effective and innovative method to determine the molecular weight of an oligonucleotide

Who Should Attend
• Chromatographers, method developers, and process engineers who are involved with the development of purification processes, as well as the analysis, of oligonucleotide therapeutics

Presenters
Bill Evans
Process Chromatography Technical Specialist
Tosoh Bioscience LLC

Moderator
Rita Peters
Editorial Director
BioPharm International

For questions or concerns, email mdevia@mmhgroup.com.

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Presented by
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improve sustainability, OptumRx, a pharmacy care services provider, has transitioned from rarely recycled foam packaging to recyclable packaging made from renewable cotton-based Kodiakotton from Kodiakooler, which was recently acquired by Airlite Plastics. The Kodiakotton insulating material is biodegradable, compostable, reusable, and recyclable. OptumRx projects the new packaging will save millions of gallons of water, pounds of carbon dioxide, and kilowatt-hours of energy (3). "OptumRX has had great success with our sustainable products," reports Corbin. “Part of the initiative is ongoing education for their consumers on the benefits of recyclable materials,” he adds.

In addition to Kodiakotton liners, Kodiakooler offers the patented Kwikpack system. This is a bundled kit of two Kodiakotton liners with an easy-to-remove, recyclable band. The liner bundle cuts insertion time and results in a packout-ready shipper in less than six seconds (4).

Fiber-based options, which can be recycled in the corrugated or waste-paper streams, also are popular. To address this market, Thermo Fisher Scientific has developed the Invitrogen Paper Cooler. The 100% paper alternative to EPS foam coolers meets thermal requirements for overnight shipments (5). Another paper-based product, ClimaCell insulation from TemperPack, is designed to replace EPS insulation and reduce packaging waste. In addition to being recyclable in the corrugated stream, the ClimaCell material protects temperature-sensitive shipments for up to 80 hours. The material also is moisture-resistant and can be customized with printed graphics/messages (6).

Another player in the insulation market, va-Q-tec, has opened a US headquarters and production facility in Langhorne, PA, to manufacture its small boxes and containers. The location also serves as a rental and repair station. The company, which is headquartered in Germany, specializes in vacuum insulation panels and phase-change materials that offer five-day temperature protection without the need for external energy sources. A rental service business offers a fleet of cold-chain containers and boxes (7).

Reuse is possible with the AcuTemp Plus Series of shippers from CSafe Global through its Repaq program. Proprietary, high-performance ThermoCor vacuum-insulated panels control payload temperatures. Simple to deploy, the shipper are available in multiple sizes and temperature profiles with integrated track-and-trace options (8).

Although reusable packaging has gained ground, one-way shippers remain a viable choice and continue to evolve.

Although reusable packaging has gained ground, one-way shippers remain a viable choice and continue to evolve. AeroSafe Global, a supplier of reusable shippers, has added a disposable option to its portfolio. The A20 insulated shipper is designed to serve shipments needing protection for 24 to 48 hours. It is fully prequalified to ISTA 7D summer and winter profiles. Minimal components simplify packouts (9).

Gore Sta-Pure flexible freeze containers from Gore PharmBIO Products are designed to protect high-value bulk drug substances from container breakage or leakage during frozen handling. “Traditional single-use bags are constructed from materials that typically become brittle when exposed to temperatures below -40 °C, which can lead to cracks or leaks in the bags,” explains Cintavy. The proprietary high-strength fluoropolymer material used for the Sta-Pure flexible freeze containers is durable after freezing at -86 °C (-123 °F) and offers the convenience and scalability of a single-use system that efficiently uses freezer space. In addition to durability, the container’s chemically inert, biocompatible, high-purity fluoropolymer composite film has a low extractables profile (10).

Gore Sta-Pure flexible freeze containers come in sizes from 50 mL to 12 L with tubing and connector options to meet different pharmaceutical and bioprocess applications. A hard-shell carrier is available for easier handling. If carbon dioxide or oxygen permeation is a concern, an optional, vacuum-sealable, secondary barrier wrap minimizes ingress (11).

Reed-Lane recently added cold storage (2–8 °C) capabilities and a dedicated climate-controlled room for vial and ampule kitting, shown in Figure 1, at its packaging facility in Wayne, NJ. Temperature and humidity sensors constantly monitor the cold storage area to document conditions and ensure there are no product-damaging temperature excursions. “Most crucially, our environmental monitoring solutions are able to provide email alerts should any specified environmental conditions be exceeded,” says Luke. He explains, “Additional sensors are deployed to provide alerts pertaining to … power outages, which would result in an immediate onsite power generator startup to maintain specified temperature continuity.”

The dedicated room for kitting temperature-sensitive products includes space for labeling vials and ampules and assembling them with other components such as printed literature. Its location adjacent to the cold storage
Introductions from Pelican BioThermal include a new version of its ProEnvision web-based asset management track-and-trace software, which allows integration of its CoolPall Flex bulk shipper into the Internet of Things. The CoolPall Flex shipper serves refrigerated, frozen, and room temperature ranges. A high level of flexibility allows the system to address different time, weight, and payload requirements.

For cryogenic products, SAVSU Technologies has expanded its portfolio of dry vapor shippers, which maintain biologic payloads at -196 °C during storage and transport. Positioned between the DV4 and the DV10 shippers, the DV7 unit offers seven days of thermal autonomy and a more compact form factor with a payload capacity similar to the DV10 shipper. With its smaller size, the DV7 shipper is easier to handle and store and less expensive to ship (12).

Cryoport Express Advanced Therapy Shippers from Cryoport have been developed to meet demand from bio-pharma customers and in anticipation of more stringent government regulations. The shippers are dedicated to human use and certified as such. Validated to ISTA 3A and 7E Transportation Standards, a new vapor plug design further doubles the holding time if shippers are mis-orientated during transit. The shippers also provide complete traceability of use history and assurance that each dewar is requalified for each trip for physical suitability, cleanliness, liquid nitrogen capacity, and shipment hold times. Validated cleaning processes reduce the risk of cross-contamination during use, delivery, and distribution (13).

REFERENCES

On Point: Biologics Drive Growth in Pre-Filled Syringes

As a result of the rising use and development of biological drugs, the biopharma industry is witnessing an increase in the adoption of prefilled syringes. The overall prefilled syringes market is forecasted to be worth nearly $10 billion by the year 2025, according to market research (1), driven in part by the rise in use of biological drugs.

“There are definitely more prefilled syringes compared to 10 years ago,” confirms Gregory Sacha, senior research scientist, Baxter BioPharma Solutions. “This is certainly due to the increase in therapeutic biologics.”

Another reason, in Sacha’s opinion, for the growth seen in the prefilled syringes market is the expanding ophthalmic market, where drugs are intended for injection into the eye for the treatment of macular degeneration and other complications related to aging and diabetes. “The volumes for injection into the eye are very low, around 20 µL to 30 µL,” he explains. “The low volumes are challenging to draw into syringes; therefore, prefilled syringes make it easier to deliver the intended dose.”

By removing the requirement of larger overfill volumes, such as those required when using vials for example, there is less waste of the drug solution with money and materials being saved when using prefilled syringes, asserts Sacha. These cost savings and reduction in waste are key advantages of prefilled syringes, in addition to patient convenience, as the dose is already prepared and ready for administration, he adds.

A VARIETY OF CHALLENGES

“Biologics as proteins by their very nature create a variety of challenges with respect to subcutaneous delivery via a prefilled syringe,” says George I’ons, head of product strategy and insights, Owen Mumford Pharmaceutical Services. “These challenges include the potential for interactions with many substances, which is why glass has historically been the material of choice for primary containers, including prefilled syringes. However, due to technological
advances in polymer chemistry, plastic prefilled syringes are now beginning to emerge on the market.”

Looking beyond glass and plastic, I’ons notes that prefilled syringes comprise other materials that can also interact with biologic therapeutics. For example, tungsten—frequently used for needle mounting—and silicone—routinely applied in formulations to the syringe barrel for lubrication of the plunger—can interact with biological substances. “Newer innovations in syringe technology are exploring ways to limit or remove these substances,” I’ons states.

Common materials used for prefilled syringes include cyclic olefin polymer, cyclic olefin copolymer, polypropylene, and polycarbonate, adds Sacha. “However, there are less advances in the materials of construction than there are in the types of syringes that are available,” he says. “For example, there are syringes in development that require substantially lower overfill volumes. There is also a syringe in development that consists of multiple layers that include an oxygen barrier. And, there are needles available with narrow diameters to reduce pain upon injection.”

SAFETY CONSIDERATIONS

When formulating biologics, the solution can often be highly viscous, which leads to specific challenges in terms of administration via prefilled syringes. “Viscosity can impact variables such as force to inject, dose delivery time, and needle gauge which all need to be determined and tested,” states I’ons.

Agreeing, Sacha emphasizes that although there is less concern for breakages with syringes than glass vials, viscosity can cause difficulties and, as a result, early studies often include flow of the solution through the needle intended for use and conducting break force and glide force studies to monitor the pressure needed to initiate movement of the plunger and continuation of the movement.

“Additionally, challenges with biologics filled into syringes typically include possible interactions with the molecule and silicone used to lubricate the barrel of the syringe and the needle,” Sacha continues. “Interactions with silicone can lead to the formation of aggregates.” Aggregates are well known to have a negative impact on the efficacy and safety of biologic drugs, potentially giving rise to harmful side effects for patients.

Discussing the intricacies of combination products, I’ons adds that human factors (HF) are essential considerations in the development and regulatory approval processes. “A rigorous HF process is key to understanding..."
user interaction and shaping user-centered risk management relating to the drug delivery device,” he says. “HF will examine the device in a series of use scenarios with a sample of all intended users, including those with impairments, to ensure safe and effective use.”

In I’ons opinion, a key safety consideration for combination products using prefilled syringes is effective needle shielding, which also requires companies to be compliant with needlestick prevention regulations that are in place in the United States (2) and Europe (3). “These regulations are key with respect to preventing transmission of bloodborne viruses such as HIV and hepatitis C,” he notes. “The regulations state that employers are responsible for the safety of their staff whether in an acute hospital setting, an alternate site, or domestic home environment. Therefore, designs that incorporate automatic or passive deployment of the needle shielding during use are seen as advantageous as no additional steps are required by the user as part of the routine injection procedure.”

**TESTING FOR SAFETY**

“Injection devices that contain drugs and biologics are known as combination products and have a specific regulatory pathway via the FDA for the US market,” explains I’ons. “In the European Union (EU) no such category exists at present, although there is ongoing work to create one, so drug-device combination products are still approved as medicinal products.”

For combination products, it is necessary for companies to ensure all necessary development and testing are performed on drug delivery devices, as would be the case for any medical device, to ensure safety. “Testing is required even though drug delivery devices are not subject to the usual regulatory approvals, such as 510(k) in the US market,” confirms I’ons.

Components of both the syringe and plunger should be tested for any extractables and leachables, notes Sacha. “The materials are often complex mixtures that have the potential to interact with certain components in the injectable formulation,” he says.

Additionally, once the components of the device have been filled, then break force or glide force studies can be conducted, which allow companies to ensure that the prefilled syringe functions correctly. These studies are also performed at certain time points during stability testing, Sacha remarks.

Testing, such as for biocompatibility, aging studies, and transit testing, along with normal validation and verification sequences, forms part of the routine development process for combination products, I’ons continues. “The goal is always to demonstrate that the final combination product is safe for the end user,” he says.

**EMERGING SOLUTIONS AND TRENDS**

As a result of challenges during formulation development of biologics or biosimilars, many companies are considering and developing higher volume prefilled syringes, asserts I’ons. “Therefore, the industry is seeing a projected increase in demand for prefilled syringes with a volume greater than 1 mL (which is the common volume used), typically to a volume of 2.25 mL,” he notes. “Consequently, prefilled delivery devices for 2.25 mL primary containers are now starting to emerge on the market, most of which are also incorporating needle stick injury safety features.”

Moreover, with the upswing in trend for increased volumes, industry is also witnessing growing interest in wearable drug delivery devices. “These wearable devices can potentially accommodate volumes in excess of 10 mL,” says I’ons.

Other solutions in development, and also some that are already on the market, are silicone-free syringes and needles with reduced amounts of silicone, adds Sacha. “Both solutions can be helpful for reducing interactions with the molecule and silicone,” he says. “In addition, using less silicone on needles can prevent, or at least reduce, the amount of silicone that is deposited in the injection site, which is particularly useful in intraocular injection.”

Discussing drug delivery devices further, I’ons reveals that there are several trends taking place and emerging within the industry. “Many companies are working on designs for connected devices, which allow the transmission of key usage data from the device to the pharma company and third parties, such as payors,” he says. “In addition, the use of devices connected to apps creates an opportunity for pharma to provide the patient with education, training and support around their medication and disease management. It is hoped that provision of this type of information will aid compliance and ultimately may positively impact patient outcomes.”

Furthermore, I’ons points out that there is an increasing focus on sustainability. “This focus is also resulting in pharma companies examining the number of disposable devices they market and therefore looking at alternatives such as reusable devices to help reduce waste,” he summarizes.

**REFERENCES**


Technology transfer of bioprocesses, while common in the biopharmaceutical industry, can be complex and present numerous challenges. Projects with accelerated development timelines that also involve multiple contract service providers have the potential to magnify the difficulties. Both contract manufacturing organizations (CMOs)/contract development and manufacturing organizations (CDMOs) and sponsor companies can facilitate the process using pragmatic approaches that mitigate risks and ensure cooperation between all parties involved.

MATERIAL, SPECIFICATION, AND CHANGE-MANAGEMENT ISSUES

When transferring a bioprocess to a CDMO, manufacturers often face multiple challenges that can include meeting the material demands of their clinical or commercial strategy and achieving aggressive timelines. These constraints must be met while accommodating the facility fit and scale-up needs determined by both the established process and the CDMO’s platform, equipment, and capabilities, according to Frank V. Ritacco, director of scientific and technical affairs for pharma services at Patheon, part of Thermo Fisher Scientific.

Abel Hastings, director of process sciences at Fujifilm Diosynth Biotechnologies, adds there are some themes that often slow the progression of sponsor projects, including materials challenges, specification ambiguity, and challenges with historical change management. “The implications of an ill-selected material can linger and hinder manufacturability. Once selected, materials dogma can be difficult to unpick because of the fear of the unknown,” he notes.

With respect to specifications, Fujifilm splits them into two general categories: safety/efficacy and manufacturability. It is important, according to Hastings, to convey the known safety/efficacy limits as early as possible and communicate what events might cause specifications to change. “As a CDMO, our primary goal is often to adjust the process...
design to reliably meet these specifications, and knowing the status of specifications up-front helps us guide our clients,” he explains.

Issues can arise, however, if sponsors establish specifications that are rooted in manufacturability too early and then the process performance changes in the development stage or when moving a program from one site to another. Establishing expectations for process performance with limited data can, Hastings says, often over-constrain the development team, leading them to necessarily forego improvements in order to achieve a manufacturability specification.

Change management during process development, meanwhile, can challenge both sponsors and CDMOs as they work to expedite processes. “In this day and age of accelerated processes and ever-changing team members, capturing rationale for change becomes increasingly important to guard against knowledge loss as team members leave a company and to help guide development in an unemotional manner,” Hastings asserts.

While commercial processes typically have robust quality and change-control systems, earlier-phase projects can often change quickly and with limited traceability. “We recommend taking a balanced approach in order to capture pertinent information while not hindering development,” comments Hastings. Some sponsors use iterative risk assessments or failure mode and effects analysis tools to quickly capture changes and build catalogs of development and lifecycle changes. “This approach allows the user to both convey historical details and to project forward-looking risks in order to steer development in a planned way,” Hastings observes.

PHASE-RELATED CHALLENGES

The overall challenge in tech transfer is to ensure that the sponsor’s process will be reproduced in a similar, robust, and compliant way. Manufacturing product in the quality and quantity in the defined timeframe are indicators of a successful transfer of the manufacturing process to the CMO/CDMO, according to Andrew Bulpin, head of process solutions at MilliporeSigma. “This overall challenge,” he says, “is mainly linked to the process itself, but it also relates to the capacity to transfer the process knowledge built for several years to the CMO/CDMO that will be integrated to ensure a successful tech transfer.”

It often also varies depending on the development phase of the bioprocess being transferred. Sponsor companies’ early-phase programs are typically challenged by transferring processes that do not fit into their external partners’ platform operations, according to Emily Schirmer, senior director of process development at Catalent Biologics. “Those partners that can offer a high level of flexibility and unit operation expertise are more successful in accommodating unique or non-traditional processes,” she remarks.

In addition, as programs progress through clinical stages, process transfer becomes more difficult because there is less inherent flexibility allowed and process changes or adaptations become more challenging to justify, Schirmer adds. Bulpin agrees that the process parameters in Phase I or II can be slightly adapted or adjusted to ensure a successful tech transfer, while in Phase III the process is more locked with defined critical process parameters, critical raw materials, and designated critical quality attributes (CQAs). Thus, any changes in Phase III should be assessed, justified and, if necessary, validated.

SCALE-UP, EQUIPMENT, AND PARAMETER ADJUSTMENTS

Adding in a scale-up element when transferring a process increases the overall risk for project success and comparability. “It is difficult to discern the differences observed from facility to facility and any disparities that can be observed on scale up independently,” Schirmer says. “These risks,” she notes, “can be minimized by having a good depth of knowledge of the facility’s specific equipment and well-established scaling models.”

Variations in equipment and material handling at facilities can complicate the tech transfer process, agrees Bulpin. “If the target facility uses different equipment, the raw materials must be compatible with that equipment,” he explains. In addition, to ensure a successful scale up, it is critical that raw materials are available at large scale and equipment capacity is evaluated. “The scale-up strategy of the CMO/CDMO, as well as its expertise in various process types, molecules, and innovative process methods—including perfusion, precipitation, and single-pass tangential flow filtration—is also key,” asserts Bulpin.

For cell-culture processes in particular, scale up can be challenging because scaling to larger volume is not linear, and multiple engineering parameters must be optimized to match process performance developed at the bench scale and confirmed at pilot to manufacturing scales of 2000 L and beyond, according to Ritacco. Harvest and downstream purification processes also need to be scaled up to match product quality and impurity profiles, and sometimes adapted to address differences in product titer and impurity profiles observed at larger scale.

Even if projects don’t involve scale-up, generally they still require a thorough investigation of which parameters need adjustment to fit best within the CMO/CDMO facility and equipment constraints without impacting specifications, Hastings observes. “In our view, scale changes and facility-fit adjustments are not complications but rather just part of what we do,” he says.
cial approval for breakthrough therapies, the time it takes to develop a bioprocess that will be robust, scalable, and reproducibly deliver target product quality remains significant, according to Ritacco. “Fast-tracking the timeline and schedule without compromising product quality and patient safety is an additional challenge,” Bulpin says.

While some product development steps can be reduced, Bulpin insists that risk analysis and decision justifications should not be underestimated. “Sufficient understanding of the process is necessary to ensure control of operating parameters to consistently deliver safe and efficacious product to patients, and achieving this on an accelerated timeline requires a skilled team leveraging well-established processes and methods, as well as past experience to streamline development and avoid pitfalls,” adds Ritacco.

It is also extremely important for sponsor companies to work with a partner who has extensive experience with tech transfer and scale up into commercial launch, according to Schirmer. “A typical program with an external partner is designed to have a process-acquisition phase, which includes a paper transfer followed by establishing the process at a small scale. Then the scale up occurs within the facility infrastructure. These scale-up activities can, however, be minimized by performing the process acquisition at the manufacturing scale to meet accelerated timelines,” she says.

Fujifilm often observes three particular challenges with accelerated programs: prioritization, collaboration and communication, and planning. Most sponsors with accelerated designations greatly reduce timelines, Hastings says, by focusing on refining their processes to reliably achieve CQAs, often at a cost to the yield. “The most successful projects have a cross-functional team that is clear on their priorities and what success looks like. Ensuring all members of the team work together to settle on the right balance of yield and CQA reliability will ensure teams aren’t derailed by conflicting priorities,” observes Hastings.

One problem Hastings has observed, however, is that as teams turn attention to accelerating development timelines, they have a tendency to unintentionally reduce the circle of communication. “The most successful teams, however, enlarge their circle to engage all functional areas, allowing everyone to be part of the process of building the best balance of speed, reliability, and risk,” he asserts.

Planning for an accelerated designation project, meanwhile, requires a balance of creativity, dedication, and pragmatism, according to Hastings. “Teams need to be able to challenge their platform expectations to strike a balance to improve timelines. This planning cannot be done once, but...
rather needs to evolve as the scientific understanding of the process grows and teams need to be aware that any new data might require an adjustment to the project plan,” he adds.

ENGAGING WITH MULTIPLE OUTSOURCING PARTNERS

For many projects, it is necessary to transfer a bioprocess from one CMO/CDMO to another. Regardless of the reason, it is essential that everyone involved does not overlook the complexities associated with leveraging previous data and maintaining technical continuity, according to Hastings.

To proactively address this issue, Fujifilm identifies new, unique, or difficult (NUD) elements, such as process-specific factors that depend on equipment idiosyncrasies that may not be fully evident to a sponsor while the process is running at a CDMO. “When a process is moved from one CDMO to another, the receiving site rarely has access to complete equipment-specific details, which can make interpretation of previously generated data challenging and incur risk,” Hastings says.

“At Fujifilm, we work hard to identify NUDs as early as possible and then categorize them as equipment-specific versus equipment-agnostic. This approach allows us to suggest studies that may improve facility fit,” he adds.

Differences in equipment throughout the process, as well as differences in scale, require optimization of multiple engineering parameters to match process performance in cell-culture, harvest, and downstream purification processes between facilities, Ritacco agrees. He also points out that analytical methods have to be transferred, established, qualified, and ultimately validated to assure consistency in analytical results between manufacturers.

Hastings also notes that some processes include historical elements that are difficult to translate into and out of batch records. “In some cases, sponsors deal with this issue by maintaining some of the same staff throughout transfers to minimize the chances that so-called tribal knowledge is lost,” he observes.

Transparency between all team members, adds Schirmer, can actually be the catalyst to a successful development, scale-up, and tech transfer of a drug with an accelerated approval designation. “Whether the process technology transfer occurs between the sponsor company and the external partner, or between two external partners, the importance of transparency is the same. Communication is also critical. If all parties are aligned and understand the path forward, it is much more likely that the transfer will be a success,” she comments.

The general constraints are the same for any tech transfer process, including those between outsourcing providers, although the confidentiality becomes more marked and the training process can be slightly different. “The aim remains the same,” Bulpin says. “In addition, any process, analytical, equipment, raw material, and/or regulatory gaps should be listed and mitigated to meet specifications and ensure a successful tech transfer.”

MINIMIZE RISK FOR OPTIMUM SUCCESS

Technology transfer introduces additional risk to the development and commercialization of biopharmaceuticals, so minimizing risk is fundamental to successful technology transfer of bioprocesses.

A clear project plan with milestones that are mutually agreed upon sets the stage for a successful program, Schirmer observes. “Risks should be identified at the onset of the project and continuously re-evaluated to determine effectiveness of mitigations and any additional risks,” she says. In addition, risk assessments should be backed by scientific reasoning and process data.

The main strategy, according to Bulpin, is to consider tech transfer—with or without scale up—as an entire project with dedicated subject matter experts, communication flow, clear responsibilities, and planning. Dedicating one individual to the management of one CMO/CDMO group helps with this approach, except for quality assurance and regulatory topics, which Bulpin says should be managed globally to ensure process compliance.

The preparation and review of thorough process descriptions, facility fit, and tech transfer documentation, with appropriate quality review and oversight, go a long way toward achieving a successful tech transfer, adds Ritacco. The experience and expertise of the teams involved is also critical. “A highly skilled and experienced team will anticipate potential challenges and leverage their deep understanding of bioprocess development, tech transfer, and manufacturing to achieve the desired process performance and product quality in a new facility, even when the timeline may be challenging,” he asserts.

It is also important, according to Hastings, for everyone involved in a tech transfer project to recognize up-front that priorities may change during the development cycle for biologics with accelerated approval designations. Risk-based tools can be used to segment process characterization into two or more phases and to design the process to prioritize CQAs over yield. “Using this approach, it is possible for sponsors to start their process performance qualification (PPQ) in parallel with some process characterization work, thereby shortening the timeline from clinical manufacturing to PPQ,” Hastings observes.

On the other hand, it can result in post-approval yield fluctuation, which makes business-planning difficult. Fujifilm sees this issue as an opportunity to move through a natural transition point. “Purposefully pivoting from biologic license application-enabling activities to business-enabling process improvements at the optimum time will allow programs to benefit from both accelerated PPQ and long-term commercial pay-back,” he concludes.
Lower Taxes, More Flexibility Crucial to Retaining Pharma Employment

As politicians focus on drug cost reduction, biopharmaceutical companies in the US are moving to states with lower taxes and relocating some facilities that had been offshore.

AGNES SHANLEY AND LAUREN LAVELLE

Public pressure to reduce drug costs has led to a number of proposals to reduce drug prices. Among the alternatives discussed so far have been de facto price controls and syncing prices with those in other global markets. In December 2019, the United States Department of Health and Human Services introduced a Safe Importation Action Plan outlining two pathways for allowing the safe reimportation of lower cost drugs from Canada (1).

Although these proposals have not yet become law, biopharmaceutical company executives are reacting to regulatory uncertainty by focusing more intensely on reducing operating costs, according to John Boyd, CEO of the Boyd Company, a site selection advisory company. “Operating costs have always been important for life-sciences site selection, but they’ve never been as important as they are now, as the industry focuses on price reduction. Many of our pharma clients see site selection as a preferred market-based way to reduce operating costs,” he told BioPharm International.

Operating costs vary highly among major life-sciences sites, and labor costs make up roughly 60% of those costs, says Boyd. In the US, Austin, TX, and Raleigh, NC, are currently among the fastest growing metropolitan areas, and both are attracting biopharma investment. So far, the Raleigh-Durham area in North Carolina offers the lowest operating costs of any US location, Boyd says, and boasts the presence of some leading universities such as Duke, University of North Carolina, and North Carolina State. Eli Lilly recently selected Raleigh as the location for a new $474-million, 462-employee facility to manufacture injectable and other diabetes therapies (2). The Austin area, meanwhile, is seeing increased investment in biopharma, due to life-sciences developments such as the University of Texas’ Dell Medical Campus and facilities affiliated with nearby Texas A&M.

Bill Bullock, the senior vice president for economic development and statewide operations at the North Carolina BioBusiness...
Biotechnology Center in Durham, NC, referred to the life-sciences hub as a “good investment” for the state. “Agriculture was, and remains, the state’s largest revenue producer. So that became a natural sector to absorb gene-based and other new technologies,” he says. “Concurrently, the state tweaked its educational infrastructure to prepare a workforce to handle tabletting and fill-finish where textiles and furniture once reigned. Thus, the foundation for a biomanufacturing bonanza that has even evolved into global leadership in gene and cell therapy manufacturing.”

North Carolina also offers incentives for companies looking to house their sites in the life-sciences hub, according to Bullock. They include a job development investment grant, the One North Carolina Fund, both discretionary performance-based programs to respond to job creation projects, and public infrastructure and transportation programs.

“Incentives provided by local units of government are key components of a broad incentives package that can help companies expand or relocate. Most are based on investment, anticipated taxes, and/or the number of jobs to be created,” Bullock says. “North Carolina offers life-sciences companies an educated workforce, access to hundreds of life-sciences companies and service providers, a well-established supply chain, and a creative and competitive landscape to support location costs and facility expansion. It’s the best value in biomanufacturing.”

Boyd’s latest analysis compared major operating costs in 2019 for a representative 300,000-ft³ biomanufacturing facility employing 300 hourly staffers (3). Examining costs for 25 US, European, and Asian locations, research found that they ranged from $58.7 million in Copenhagen to $13.7 million in Bangalore. In the US, costs ranged from $55.4 million in New York to $37.2 million in Raleigh/Durham, NC.

“In the US, there has already been a mass exodus of human capital to states that have right-to-work laws,” says Boyd. These laws establish “at will” employment and make membership in labor unions voluntary, reducing union power as well as labor costs for employers (4). There has also been a trend to “reshore” some operations and bring them back to the US in lower-cost labor states, he says. “For areas such as Bangalore in India, the initial numbers may be compelling, but investors have found additional hidden costs,” he says, including training, and, in the US, boosting corporate participation in federal procurement programs has become a political issue that has both Republican and Democratic party support, he says. Boyd notes that new life-sciences regional hubs may be on the horizon, depending on how new regulations take shape in the US. Amgen, for example, is building a new 1600-employee facility in Greenwich, RI. Other potential areas for future development could include Southern Florida, Phoenix, AZ, Las Vegas, NV, and the Winston-Salem area of North Carolina near Wake Forest University.

HOLDING THE LINE ON MORE STATE TAXES

In the meantime, many municipalities are getting the message loud and clear, to hold the line on new corporate taxes, says Boyd. New Jersey, which is the nation’s largest biopharmaceutical and pharmaceutical development and manufacturing center, may offer a cautionary tale.

The state recently increased corporate and personal income taxes, on top of high property taxes, making it more difficult for companies located in the state to remain competitive and reducing disposable income for working professionals, says Boyd. Over the past 15 years, he noted in a December 2019 interview (5), higher taxes in the state have resulted in $30 billion in personal income moving to lower cost, more corporate friend locations. New Jersey officials have also proposed a millionaire’s tax that would impose 10.75% in income tax on individuals earning $1 million per year or more. The proposed regulations could affect 20,000 state residents, many of them business owners, and could decrease investment in the state. New York, California, and Massachusetts already have similar laws in place.

As for North Carolina, the state’s 2.5% corporate income tax is the lowest rate of states that levy this tax, according to Bullock. It also boasted the seventh lowest commercial and ninth lowest industrial effective property tax rates in the country in 2017.

“The state offers a number of sales and use tax exemptions,” Bullock says. “For example, in 2018 North Carolina significantly increased long-term business cost savings through single sales factor apportionment for multistate corporations. There are also exemptions for manufacturing machinery and related equipment, as well as raw materials, fuel, piped natural gas, and electricity used for manufacturing. Other exemptions and credits are available for R&D and software publishing, pollution abatement equipment, recycling, and historic preservation.”

REFERENCES

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The global coronavirus pandemic has forced the postponement of many industry events. The dates listed below reflect the scheduled and rescheduled dates for major bio/pharma industry events as of March 25, 2020. For the latest information, contact the event organizer, or visit www.BioPharmInternational.com/events.

**BIO International Convention**
*June 8–11, 2020, San Diego, CA*
www.bio.org/events/bio-international-convention
Hosted by the Biotechnology Innovation Organization, the event features more than 1100 biotechnology companies, academic institutions, state biotechnology centers, and related organizations across the US and in more than 30 other nations.

**CPhI China**
*June 22–24, 2020, Shanghai, China*

**CPhI Southeast Asia**
*July 1–3, 2020, Bangkok, Thailand*

**CPhI North America**
*Sept. 9–11, 2020, Philadelphia, PA*

**CPhI Japan**
*Sept. 30–Oct. 2, 2020, Osaka, Japan*

**CPhI Worldwide**
*Oct. 13–15, Milan, Italy*

**INTERPHEX 2020**
*July 15–17, 2020, New York*
www.interphex.com/Register/INTERPHEX is the premier pharmaceutical, biotechnology, and device development and manufacturing event where you can “Experience Science through Commercialization.”

**69th PDA Annual Meeting**
*July 20–22, 2020, Raleigh, NC*
www.pda.org/conference/2020-pda-annual-meeting/home
This year’s event theme will be “Enhancing the Future with Innovative Medicines and Manufacturing” and the meeting will feature plenary and group sessions focused on developing new modalities, targeting real-time and parametric release, engineering data solutions, and modernizing products and manufacturing.

**AAPS 2020 PHARMSCI 360**
*October 25–28, 2020, New Orleans, LA*
www.aaps.org/pharmsci/annual-meeting
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Both sponsors and CMOs/CDMOs must have an active role, according to Schniepp. “The specific level of involvement of the sponsor may depend on the confidence they have in the CMO/CDMO organization. The CMO/CDMO should make sure they involve the sponsor in decisions involving material quality so the sponsor is aware of the impact on their product,” says Schniepp.

ENSURING QUALITY IS ABOUT VIGILANCE

Maintaining a safe supply chain is crucial in the bio/pharmaceutical industry. The efficacy and safety of the materials used in drug products is of utmost importance. And it is the sponsor’s responsibility to ensure the quality of all materials used in their products. Sponsors must not rely on others to ensure quality, says O’Connor. Also, not all suppliers should be treated the same. “Clearly, some suppliers have greater risk than others, either based on the product type, location, etc. These suppliers should receive more scrutiny,” she says. Sponsors also must not cut corners or do what is convenient, says O’Connor. For example, she notes, it is inconvenient, but necessary to audit suppliers in China and India. In addition, sponsors should also not make supplier decisions based on price or availability instead of quality and safety, says IPEC-Americas.

Communication is key to supplier oversight, says Schniepp. “Both parties need to be willing to talk as frequently as needed to address issues before they manifest into a disruption in the supply chain. The frequency of these conversations are not necessarily defined in a quality agreement. They are important in establishing an open relationship between the supplier and the purchaser so issues can be solved before supply chain disruption occurs. Not all problems can be solved through the terms included in the quality agreement and both parties must be willing to work outside the defined ‘communication schedule’ of the quality agreement to avoid unnecessary supply-chain interruptions.”

REFERENCES


5. FDA, 21 CFR 211.84(d), Title 21–Food And Drugs, Chapter I–Food And Drug Administration, Department Of Health And Human Services, Subchapter C–Drugs: General, April 1, 2019.
Ask the Expert — Contin. from page 58

and identifies gaps so the company can implement changes to ensure continuous improvement.

AGING FACILITIES

Aging facilities are of concern because they can lead to drug shortages. It is hard to achieve compliance to current regulatory expectation when manufacturing new and novel products on manufacturing lines that are more than 30 years old and the analytical results rely on outdated methodology (5). The age of the line usually indicates that the processes being run on those lines are non-automated and require human driven steps. In these situations, it is critical a company demonstrates it has a quality mindset because of the human/product interface. The best way to address this issue in an inspection is to demonstrate that the company has a plan to update its facility over time. The plan should indicate what needs to be updated and a timeline for implementation.

INVESTIGATIONS/CAPA

The need for a robust investigation/CAPA process is clearly defined in global regulations, but it seems the industry still struggles with conducting and documenting root cause when it comes to investigations based on FDA 483 observations (6). The purpose of an investigation is to identify the root cause of a deviation and take appropriate action to correct the issue across the manufacturing/product line. The best way to demonstrate proper control of this process during an investigation is to ensure you have a robust investigation process, which routinely identifies root cause and that once the correction is made, it does not recur (7). The ability to demonstrate this depends on the understanding and training of the people involved in the investigation process and data that shows the problem was addressed and solved (8, 9).

RISK MANAGEMENT

Every company should have a quality risk management plan (10). A well-written and well-implemented quality risk management plan is an integral and valuable element of an effective quality system. 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 (11). Having the plan available for discussion and demonstrating a knowledge of the plan, how it is incorporated into the culture, and making sure it is revised as needed to reflect current practices is critical to having a successful outcome should you be audited on this topic.

The bottom line is that the regulatory landscape is changing, and it is conceivable that companies will begin to be audited on programs and process that are more subjective than tangible. To be prepared for an audit that touches on the intangibles of a functioning quality management system, companies should begin to formulate programs and systems that address the aforementioned topics.

REFERENCES

Q: I am preparing my site for an audit and have prepared and trained our employees on the usual topics (training program, standard operating procedures [SOPs], change control, etc.). I am concerned that this traditional approach may not be enough in the current regulatory environment. Can you offer some guidance into other issues I should focus on in preparing for the audit?

A: This is a great question and shows an insight into the changing regulatory landscape. I think it will be critical in the coming years to focus on addressing certain intangible topics during routine regulatory audits. These topics should be addressed as part of your company’s overall improvement plans and programs.

I would focus on the following topics as a part of preparing for any routine audit: data integrity, quality culture, aging facilities, investigations/corrective actions and preventive actions (CAPA), and risk management. I am of the opinion that these topics will become routine areas of focus for regulatory inspections regardless of the affiliation of the regulatory authority performing the audit. These topics are not new to the industry. There has been much discussion on their impact on drug shortages. It is my opinion that developing robust programs addressing these issues and incorporating them into everyday routine operations will improve the drug shortage situation, improve a company’s operating performance, and improve the outcome of regulatory inspections for the company.

FDA has been publishing guidance on these issues over the years, and now as the agency gets ready to finalize the New Inspection Protocols Project (NIPP), it is time to revisit some of these recommendations and implement some of the advice offered. The intent of the NIPP program (1) is to provide inspectionsal assessments to support tracking and improvement of performance across pharmaceutical manufacturers and products and enhance the production, utility, and consistency of the establishment inspection reports.

**DATA INTEGRITY**

Every company should have a program to address data integrity issues that include guidance on what data integrity is, how to recognize it, how to prevent violations, consequences for violating the company’s data integrity policy, etc. The program should also address the frequency and effectiveness of employee training on this topic. The program should demonstrate an understanding of regulatory expectations as well as an explanation of how those expectations are incorporated into the data integrity program. The program needs to go beyond the concepts of ALCOA (attributable, legible, contemporaneous, original, accurate) and include the four new attributes in ALCOA+ (complete, consistent, enduring, available) (2, 3).

**QUALITY CULTURE**

The concept of quality culture came about with the introduction of quality metrics. FDA introduced the concept of collecting quality metrics in 2013 (4). Since that time, the industry and regulatory authorities worldwide have embraced the idea that in order to rely on the metrics collected, the company needs to have a culture that supports an open, transparent reporting of “deviations, errors, omissions and aberrant results at all levels of the organization, irrespective of hierarchy” (3). There has been work done by the Parenteral Drug Association and University of St. Gallen suggesting there is a correlation between mature quality attributes and quality culture behaviors. To address the issue of a quality culture during a regulatory inspection, the company should be able to demonstrate their quality system is functional.

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