Volume 32 Number 6

BioPharm INTERNATIONAL

June 2019

The Science & Business of Biopharmaceuticals

www.biopharminternational.com

CAN NANOTECH DELIVER BIG DRUG BENEFITS?

UPSTREAM PROCESSING

STREAMLINING UPSTREAM PROCESSING: A GOOD PLACE TO START

OPERATIONS

MOVING PAT FROM CONCEPT TO REALITY

PEER-REVIEWED

COMPARING FACILITY LAYOUT OPTIONS FOR MANAGING BUSINESS AND OPERATING RISKS

AVAILABLE:
BIOPHARMA OPPORTUNITY

Biologic Manufacturing Facility - 178,713 gross SF on 20 Acres

5550 Airport Blvd., Boulder, CO 80301

ADDITIONAL INFORMATION:

- The facility is designed for cell culture production with significant investment recently made in process equipment and upgrading utilities.
- This facility houses drug substance manufacturing (two 20,000 liter bioreactors), day staging area, quality control laboratories and central utilities.
- A detached generator building was built in 2000.
- The building is optimally equipped for a user-operator looking to pursue both research and production under one roof.
- The facility offers easy access to I-25 and US Route 36. University of Colorado in Boulder and Colorado State University in Fort Collins are both within an easy commute to the site.

CONTACT DETAILS:

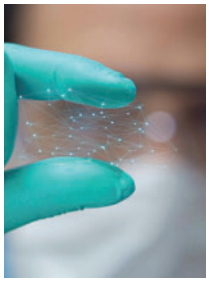
Eric Dienstbach
303.779.4345
Edienstbach@binswanger.com
www.bins.properties/bldr-BP

BINSWANGER

BioPharm INTERNATIONAL
The Science & Business of Biopharmaceuticals

BioPharm INTERNATIONAL

BioPharm International integrates the science and business of biopharmaceutical research, development, and manufacturing. We provide practical, peer-reviewed technical solutions to enable biopharmaceutical professionals to perform their jobs more effectively.



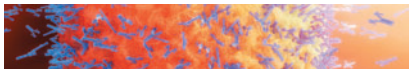
COVER STORY

10 Can Nanotechnology Deliver Big Drug Benefits?

Research advances have enabled the application of nanotechnology to drug delivery. What does this technology offer in the way of enhancing therapeutic effect?

Cover Design by Dan Ward
Image: MG - stock.adobe.com

FEATURES



DEVELOPMENT

Taking Therapeutic Antibodies to the Next Level

Feliza Mirasol

This article explores the challenges and potential of next-generation therapeutic antibodies.

UPSTREAM PROCESSING

Streamlining Upstream Processing: A Good Place to Start

Felicity Thomas

As cost and time pressures within biopharma are on the rise, innovative expression systems may offer companies a good opportunity to streamline processes early on.

DOWNSTREAM PROCESSING

Addressing the Complex Nature of Downstream Processing with QbD

Susan Haigney

Quality by design brings both challenges and benefits to the development of downstream processes.

PEER-REVIEWED

Comparing Facility Layout Options for Managing Business and Operating Risks

Mark F. Witcher and Harry Silver

The authors present a risk analysis of the impact of various business and operating risks on three facility layout strategies.

DATA ANALYTICS

From Data to Information

Agnes Shanley

Making siloed data accessible across functions and to contract partners is the first step to facilitating continuous improvement and enabling use of artificial intelligence in manufacturing.

OPERATIONS

Moving PAT from Concept to Reality

Cynthia A. Challener

The learning curve for process analytical technology has slowed widespread adoption.

SUPPLY CHAIN

On the Right Track

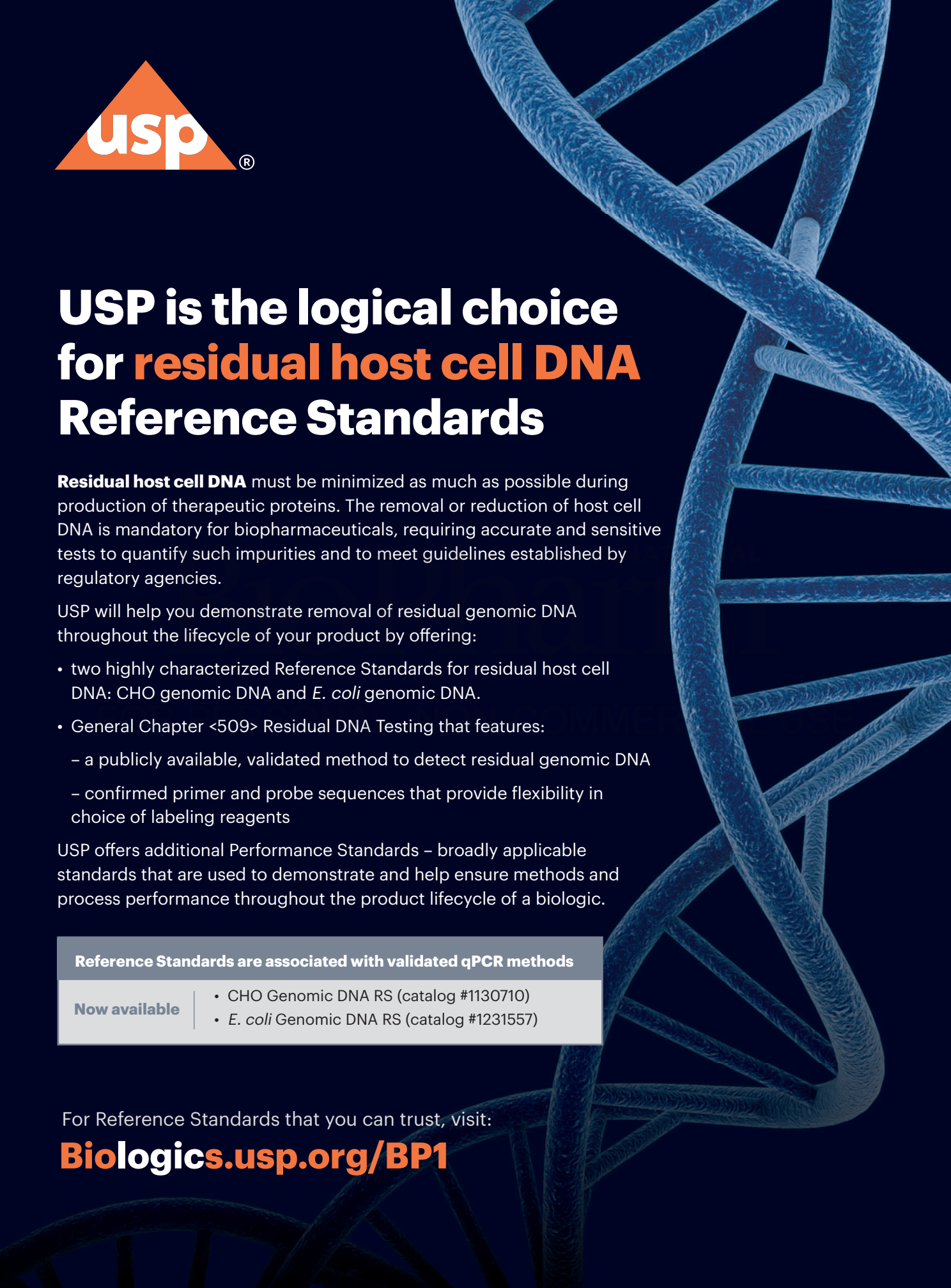
Felicity Thomas

Proactive approaches that consider long-term supply chain security compliance are recommended to ensure companies stay on the right track.

COLUMNS AND DEPARTMENTS

BioPharm International is selectively abstracted or indexed in: • Biological Sciences Database (Cambridge Scientific Abstracts) • Biotechnology and Bioengineering Database (Cambridge Scientific Abstracts) • Biotechnology Citation Index (ISI/Thomson Scientific) • Chemical Abstracts (CAS) • Science Citation Index Expanded (ISI/Thomson Scientific) • Web of Science (ISI/Thomson Scientific)

BioPharm International ISSN 1542-166X (print); ISSN 1939-1862 (digital) is published monthly by MultiMedia Healthcare LLC 325 W. First Street, STE 300 Duluth, MN 55802. Subscription rates: $76 for one year in the United States and Possessions; $103 for one year in Canada and Mexico; all other countries $146 for one year. Single copies (prepaid only): $8 in the United States; $10 all other countries. Back issues, if available: $21 in the United States, $26 all other countries. Add $6.75 per order for shipping and handling. Periodicals postage paid at Duluth, MN 55806, and additional mailing offices. Postmaster Please send address changes to BioPharm International, PO Box 6128, Duluth, MN 55806-6128, USA. PUBLICATIONS MAIL AGREEMENT NO. 40612608, Return Undeliverable Canadian Addresses to: IMEX Global Solutions, P. O. Box 25542, London, ON N6C 6B2, CANADA. Canadian GST number: R-124213133RT001. Printed in U.S.A.



USP is the logical choice for residual host cell DNA Reference Standards

Residual host cell DNA must be minimized as much as possible during production of therapeutic proteins. The removal or reduction of host cell DNA is mandatory for biopharmaceuticals, requiring accurate and sensitive tests to quantify such impurities and to meet guidelines established by regulatory agencies.

USP will help you demonstrate removal of residual genomic DNA throughout the lifecycle of your product by offering:

- two highly characterized Reference Standards for residual host cell DNA: CHO genomic DNA and *E. coli* genomic DNA.
- General Chapter <509> Residual DNA Testing that features:
  - a publicly available, validated method to detect residual genomic DNA
  - confirmed primer and probe sequences that provide flexibility in choice of labeling reagents

USP offers additional Performance Standards – broadly applicable standards that are used to demonstrate and help ensure methods and process performance throughout the product lifecycle of a biologic.

Reference Standards are associated with validated qPCR methods	
Now available	• CHO Genomic DNA RS (catalog #1130710) • *E. coli* Genomic DNA RS (catalog #1231557)

For Reference Standards that you can trust, visit:

Biologics.usp.org/BP1

Rita Peters is the editorial director of *BioPharm International*.

FDA's annual manufacturing report card shows more quality compliance is needed.

Bio/Pharma Facilities Still Have a Lot to Learn

As schools in the United States close for the summer break, student grades serve as a measure of how well teachers shared knowledge, how well students understood and retained that information, and how the school, as a whole, performed year over year.

FDA recently issued a report card of the bio/pharma industry's manufacturing quality performance. The *Report on the State of Pharmaceutical Quality* (1), issued in May 2019 by the Office of Pharmaceutical Quality in FDA, Center for Drug Evaluation and Research, assessed the ability of pharmaceutical manufacturers to deliver quality pharmaceutical products to the US market during fiscal year 2018. The report analyzed product recalls, quality defect reports, drug shortages, and application state (e.g., submissions, approvals, refuse-to-file, refuse-to-receive, and complete response letters) as a basis for its analysis.

The report examined manufacturing site data by geographic region, therapeutic category, application type, and manufacturing sector. FDA issues a site inspection score—on a scale of 1 to 10 with a higher number indicating greater compliance with current good manufacturing practices—based on FDA quality inspections over the past 10 years.

Of the 4676 sites in FDA's catalog, 42% manufacture "no application" products, such as over-the-counter products, monograph, unapproved, or homeopathic products. The remaining 58% of sites manufacture application drug products (e.g., new drug application [NDA], abbreviated new drug applications [ANDA], biologic license application [BLA], etc.) and nearly half (46%) of these sites manufacture both NDA and ANDA products.

The report noted "volatility" in the site catalog in the past year; the agency removed from the catalog "a large number" of sites in India, China, and South Korea in FY2018 because they did not make products for the US market and, therefore, did not have to be registered with FDA. This indicates "a lack of understanding of the registration and listing requirements," FDA noted in the report. The agency also reported a 32.8% net increase in the number of packaging and labeling sites—suggesting an increase in outsourcing of these functions.

Less than 40% of the drugs for the US market are manufactured in the US. India (12%) and China (11%) are the two largest offshore suppliers. FDA also noted that a small number of sites are responsible for manufacturing a large number of listed products; the number of products manufactured at a site is a risk factor used in prioritizing the need for surveillance inspections. In the US, three sites—two of which make homeopathic products—account for 9.5% of all products listed by all US sites. The number of listed products manufactured by the top three sites in China (11.2%) and India (12%) are even higher.

Inspections and grading

In FY2018, FDA conducted 1346 drug quality inspections, covering less than one-third of sites in its catalog. More than half of the inspections were outside the US. The average inspection score of 7.5 for FY2018 was down slightly from FY2017 (7.7). Sites in the European Union (7.9) and the US (7.7) scored higher than average; sites in China (7.0), India (7.0), and the rest of the world (7.2) were lower than average. Statistical differences were also noted in application areas, with sterile non- application products as one of the lowest performing.

FDA noted "… some trends highlight opportunities for increased outreach to, surveillance of, and enforcement of certain markets," indicating that for regulated drug manufacturing, school is never out.

Reference

1. FDA, *Report on the State of Pharmaceutical Quality*, May 13, 2019. ◆

FDA Advances New Approach to Drug Quality Assessment

CDER's KASA program seeks manufacturer data on drug attributes and risks to inform oversight.

As part of its ongoing efforts to ensure the availability of high-quality medicines, FDA's Center for Drug Evaluation and Research (CDER) is rolling out a new system to enhance the evaluation of prescription drug attributes, risks, and control strategies. The Knowledge-aided Assessment and Structured Application (KASA) initiative aims to improve the efficiency, consistency, and objectivity of regulatory quality assessment by collecting structured data on drug substance, product design, and manufacturing process to better assess inherent risks and how they are controlled. CDER's Office of Pharmaceutical Quality (OPQ) is piloting the program first for abbreviated new drug applications (ANDAs) for generics, with the aim of rolling out the system to generic solid oral dosage forms by year-end. Next will come generic liquids and injectables, followed by new drugs and biologics.

With more ANDAs and new drug applications (NDAs) filed each year, many involving complex therapies, and increasingly tight assessment time frames for approval set by user fee programs, CDER officials are looking for ways to evaluate submissions more expeditiously and effectively. This new approach asks manufacturers to file structured applications that present key data on product attributes, as opposed to lengthy, text-based narratives. The aim is for OPQ staffers to perform computer-aided analyses that support benefit/risk assessments for comparison across products and facilities. Under development for almost two years, the KASA initiative became more visible when it was discussed publicly and gained unanimous support at the September 2018 meeting of FDA's Pharmaceutical Science & Clinical Pharmacology Advisory Committee.

Jill Wechsler is *BioPharm International's* Washington editor, jillwechsler7@gmail.com.

> The KASA initiative aims to improve the efficiency, consistency, and objectivity of regulatory quality assessment.

CDER and OPQ leaders presented more detailed information on KASA at the April 2019 PQRI/FDA conference on Advancing Product Quality in Rockville, MD (1). KASA aims to provide a structured assessment of an application that summarizes key information and "minimizes text-based narratives," explained OPQ Deputy Director Lawrence Yu. Advances in information technology not only generate more information on key quality attributes, Yu pointed out, but also allow for a faster, more complete assessment. He directed manufacturers to an article outlining the KASA program in the *International Journal Of Pharmaceutics: X* for further information on the program and its approach (2).

Similarly, at the April 2019 CMC Workshop sponsored by the Drug Information Association (DIA), Geoffrey Wu, associate director of OPQ's Office of Lifecycle Drug Products (OLDP), described how the KASA initiative will capture and manage knowledge of drug product quality to establish a product risk control strategy for lifecycle management. This approach will avoid inconsistent application of quality standards and help prevent shortages and quality failures of marketed drugs. KASA also will assess

manufacturing risks and controls in order to "flag the potential need for a pre-approval inspection based on multiple factors and complexities using standardized risk thresholds," Wu noted. This will involve examining the control strategy for the manufacturing facility, including site inspection history, based on a standardized assessment of risks compared across products and facilities.

MORE STRUCTURED ASSESSMENTS

The modern drug assessment system under KASA will build on algorithms of risk and support computer-aided analysis for a structured assessment of an application. The process begins with an objective evaluation of risk that considers key critical quality attributes, enabling OPQ staff to then focus on more risky products. The analysis considers the severity of possible harms and the detectability of future failures to be able to compare risks across products and determine if attributes are within or outside acceptable ranges. With such information, CDER still may approve a risky product, but with a recognition of the need for greater oversight to control for possible future problems.

In making the case for KASA at the PQRI meeting, OLDP Director Susan Rosencrance observed that applications for new drugs and generics composed of unstructured text can be a hindrance to an efficient agency assessment of product quality. Too often, she said, the important information on how an applicant controls risk "is lost in hundreds of pages of text." This may encourage a reviewer's quality assessment to be more subjective, leading to inconsistent decisions by the agency.

Drug applications that present information in prose require reviewers to do "a lot of hunting and pecking" to pull out key data, added Mary Ann Slack, director of CDER's Office of Strategic Programs. To move forward, FDA plans to develop and test electronic data standards for submitting product quality and chemistry, manufacturing, and controls (CMC) data to the agency, Slack explained. This will be described in draft guidance slated for publication by March 2020 to further explain how future applications should present data files that can be entered into FDA's drug data system to check ranges and areas to review more closely.

KASA is part of broader CDER efforts to modernize its drug regulatory program. This includes reorganizing the Office of New Drugs, developing new IT platforms and applications, establishing quality metrics, and building the emerging technology program to promote new drug design and manufacturing strategies. More consistent and objective regulatory assessments under KASA fits these broader goals by helping FDA achieve more first-cycle approvals for manufacturers and more affordable and accessible medicines for patients.

REFERENCES

1. PQRI, 4th FDA/PQRI Conference on Advancing Product Quality, April 2019, https://pqri.org/4th-fda-pqri-conference-on-advancing-product-quality-presentations/
2. L. X. Yu et al., *International Journal of Pharmaceutics: X*, 1 (December 2019), www.sciencedirect.com/science/article/pii/S2590156719300246 ◆

FDA Publishes Guidance on Therapeutic Protein Biosimilars

On May 21, 2019, FDA published guidance (1) on the design and evaluation of comparative analytical studies used to support the biosimilarity of a proposed therapeutic protein product to a reference product licensed under section 351(a) of the Public Health Service Act (PHS Act). The guidance also offers recommendations on the scientific and technical information for the chemistry, manufacturing, and controls (CMC) portion of a marketing application for a proposed product submitted under section 351(k) of the PHS Act.

Among an overview of the PHS Act and the Biologics Price Competition and Innovation Act of 2009 (BPCI Act), the guidance specifically discusses expression systems, manufacturing processes, physicochemical properties, functional activities, target binding, impurities, reference products and standards, finished drug products, and stability. Considerations addressed for a comparative analytical assessment include reference and biosimilar products and data analysis.

The guidance is part of a series of documents to facilitate the implementation of the BPCI Act. Other guidance documents address scientific considerations, biosimilar development, clinical pharmacology data, labeling of biosimilars, and demonstrating interchangeability.

Reference

1. FDA, *Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations, Guidance for Industry* (FDA, May 2019).

—*The editors of* BioPharm International

Can Nanotechnology Deliver Big Drug Benefits?

Research advances have enabled the application of nanotechnology to drug delivery. What does this technology offer in the way of enhancing therapeutic effect?

FELIZA MIRASOL

Bioavailability of a drug substance is a consistent challenge in the development of both small-molecule and large-molecule therapeutics. The ability to ensure or enhance the therapeutic effect of a drug product has led to various innovations in drug delivery technology. Nanotechnology is one innovation under exploration as a potential drug delivery vehicle.

Nanoparticles hold significant potential as an effective drug-delivery system. They typically range in sizes less than 100 nm in at least one dimension and can consist of different biodegradable substances, such as natural or synthetic polymers, lipids, or metals. According to a study by S.S. Suri *et al.*, nanoparticles are taken up by cells "more efficiently than larger micromolecules and, therefore, could be used as effective transport and delivery systems" (1). By incorporating nanoparticles, drugs can either be integrated into the particle matrix or be attached to the particle surface.

Though a relatively newer science, "nanomedicine" and nano-delivery systems are nevertheless rapidly developing. Nanotechnology offers multiple benefits in treating chronic human diseases with its ability to provide site-specific and target-oriented delivery of precise medicines. There have recently been a number of applications of nanomedicine (e.g., chemotherapeutic agents, biological agents, immunotherapeutic agents) in treating various diseases (2).

Today, companies such as N4 Pharma, a UK-based pharmaceutical company specializing in a novel silica nanoparticle delivery system for vaccines and therapeutics, and Nanoform, a Finland-based company that offers services in nanotechnology and drug particle engineering, are pushing forward with their respective technology development using nanotechnology in drug delivery applications. Nigel Theobald, founder and CEO of N4 Pharma, and Gonçalo Rebelo de Andrade, chief of business operations at Nanoform, shared with *BioPharm International* the inroads these companies are making and how nanotechnology can enhance the therapeutic effects of biologic-based drugs as well as traditional small-molecule drugs.

MG - stock.adobe.com

Register by July 30 and save up to $600!

2019 PDA/FDA Joint Regulatory Conference

Manufacturing Innovation, Quality, and Compliance: Achieving 20/20 Vision

Take advantage of unparalleled opportunities to hear from and engage with regulatory and industry experts at the 2019 PDA/FDA Joint Regulatory Conference!

Stay up to date with the latest industry and regulatory advancements at this exceptional Conference!

Find out how the continuing evolution of innovative manufacturing capabilities will affect quality, compliance, and regulatory paradigms. Over two and a half days, the best in the industry will offer their perspectives on these topics and more:

- Combination products and connected care applications
- Effective internal and external audits
- Designing aseptic processes to reduce quality risk
- Data integrity remediation and an update on the associated PDA Technical Report
- Evolving approaches to quality management systems
- Improving deviation and failure investigations
- Strategies for continuous improvement of facilities and equipment

Other Conference highlights include:

- The always popular Center Updates
- **NEW TIME:** Lunch with the Regulators session
- Networking Opportunities
- Exhibition featuring product and service solutions to improve your company's processes

Join nearly 1,000 of your industry peers at this "can't-miss" event!

To learn more and register, visit *pda.org/2019PDAFDA*

CONNECTING PEOPLE SCIENCE AND REGULATION®

SEPTEMBER 16-18 | WASHINGTON, DC
EXHIBITION: SEPT. 16-17
#2019PDAFDA

FDA

PDA Parenteral Drug Association

MAKING INROADS

BioPharm: What is nanotechnology, and how is it suited to be a platform or vehicle for drug delivery?

Theobald (N4 Pharma): People started talking about nanotechnology in the context of drug delivery more than 10 years ago. However, back then it was all about legacy drug delivery technology that happened to be in the nano-size range—generally accepted to be 1 nm to 1000 nm—being applied to improve the bioavailability or negate toxicity challenges with existing small-molecule drugs. Liposomes were the hot topic, and several drugs came to market in this new dosage form.

Fast forward to today, and the discussion—as well as the technology and targets—have moved on considerably, with the majority of activity concentrated on developing improved vaccines and cancer therapeutics using DNA, RNA, or other large-molecule approaches.

Andrade (Nanoform): Nanotechnology is the science that manipulates, generates, and utilizes submicron sized materials. In the pharmaceutical space, nanotechnology is associated with the manipulation and generation of excipients. This includes silicon-based nanoparticles, lipid nanoparticles, and liposomes, which are used as formulation adjuvants and dissolution enhancers of drug substances. Through the manipulation and generation of API nanoparticles, drug molecules can become more soluble, thus enabling a faster onset, a larger therapeutic window, and reduced side effects.

In recent years there have also been initiatives to generate intelligent biomaterials (e.g., with sensors and nanotech circuits) that can be used for sustained release, adding to the already long line of existing enhanced performance biomaterials (e.g., biomaterials with silver nitrate nanoparticle deposition at the surface for medical device and implant infection reduction).

BioPharm: What is the biggest hurdle to overcome?

Andrade (Nanoform): While developing any new and innovative technology, scientists and companies alike are faced with not only the uncertainty of the success of its delivery platform (technology development risk), but also the adoption barrier associated with a lack of previous experience with the technology (market risk). In addition, given the nature of drug delivery within the pharmaceutical industry, there are safety and toxicology requirements that scientists and companies will need to comply with (regulatory risk) to obtain market approval.

Theobald (N4 Pharma): At present, our work is specific to vaccines and cancer therapeutics, and in this scenario, the drug delivery system must cope with the specific challenges of delivering nucleic acids (DNA/RNA).

A DNA/RNA drug may have relatively poor immunogenicity, and they are unstable *in vivo*. So, the goal in the body is to protect the messenger RNA/plasmid DNA (mRNA/pDNA) from the immune system and deliver it to the site of action before releasing it to stimulate an immune response, whereby the body's own systems either attack the target tumor or produce enough antibodies against it.

If you've got a DNA/RNA-based active, therefore, you're going to have to develop it together with a delivery system. In fact, there are a range of technologies that can be considered, such as drug-protein conjugates and virus-like vectors, but lipid nanoparticles (LNPs) have emerged as the most common approach to date.

LNPs meet many of the criteria mentioned above for a good drug delivery system. However, they exhibit some well-known limitations, most notably: stimulating the release of systemic inflammatory cytokines; accumulation in the liver and spleen, with resulting possibility of toxicity; low drug payload for hydrophilic molecules; drug expulsion; and reticuloendothelial system (RES) clearance for systemic drug delivery (3).

Importantly, LNPs also suffer from suboptimal cellular penetration; it is interesting to note that currently, of 23 cancer vaccines in Phase II/III trials, 18 showed low clinical effect, probably due to insufficient presentation of the tumor-associated antigens.

REGULATORY CONSIDERATIONS

BioPharm: What regulatory hurdles have to be overcome, and what kind of guidance does the industry have—or lack—from regulatory authorities?

Theobald (N4 Pharma): Neither FDA nor the European Medicines Agency (EMA) place specific barriers on a company using nanotechnology as part of its drug delivery modality, but at the same time they have not yet come to a firm view on its use because it is so novel and varied. FDA—in draft guidance for industry, published late in 2017 (4)—provides a risk-based framework that covers safety; preclinical studies such as absorption, distribution, metabolism, excretion, and toxicity; and clinical trials.

EMA's position, as presented in their Reflection Paper on Nanotechnology-Based Medicinal Products for Human Use (5), is also clear: 'As for any medicinal product, the [European Union] EU-competent authorities will evaluate any application to place a nanomedicinal product on the market, utilising established principles of benefit/risk analysis, rather than solely on the basis of the technology per se.'

In practice, both regulatory agencies are pleased to engage with a company early in the drug development process to ensure that any specific nanotechnology aspects are appropriately dealt with ahead of an application.

Andrade (Nanoform): As with every other technology that is incorporated into a drug product, the use of nanotechnology needs to provide sufficient evidence of its safety, tolerability, and the control of its manufacturability. In the spirit of collaboration with the industry that the regulatory authorities have long demonstrated, FDA's nanomaterials guidance provides additional information to the industry as to how the agency will review an application that incorporates nanotechnology into the developed drug product.

THERAPEUTIC ADVANTAGE

BioPharm: What therapeutic advantage does nanotechology offer?

Andrade (Nanoform): Nanotechnology has been traditionally associated with the pursuit of improved solubility and dissolution for poorly soluble small-molecule drugs and the generation of sustained drug release formulations. Recent advances in the generation of nanoparticles, however, have demonstrated increased biologic membrane permeability associated with nanoparticles. Greater permeability enables deeper penetration in the tumor microenvironment, leading to its increased application in oncology and the generation of more effective drug product formulations.

Nanotechnology-driven drug products have shown to have a faster onset in terms of therapeutic action, due to the increased solubility of the nanosized API. It offers a potential reduction of the daily dose required for a therapeutic effect, while also enabling a decrease in side effects associated with the drug uptake.

Theobald (N4 Pharma): In general, everyone developing drug vaccines consisting of nucleic acids is looking to achieve some or all of the following benefits from delivery systems:

- Protection of the drug substance from early or rapid degradation in the body
- Preferential delivery to the target site of action
- A combination of high loading capacity, controlled release with extended half-life, no leakage, and no interference with the stability of the encapsulated product.

In addition, good biocompatibility, low toxicity, and biodegradability, as well as a clear understanding of the mode of action of the delivery system, are desirable factors. To achieve this, many believe that nanoparticle delivery is critical to enabling these drugs to be used effectively in a therapeutic setting.

TECHNOLOGY IN DEVELOPMENT

BioPharm: Can you briefly walk us through your brand of nanotechology and where in the manufacturing process it is implemented?

Theobald (N4 Pharma): Our approach has been different and our technology—called Nuvec—is a delivery system with differentiated physical and structural properties specifically adapted to carry mRNA, pDNA, and other therapeutic proteins. Nuvec nanoparticles are hollow silica spheres covered in thin silica structures that are functionalised with polyethyleneimine (PEI) to enhance binding of macromolecules. The nanoparticles are 180 nm but can be made available from 120 nm to 500 nm in size. Its unique 'spikey' surface traps and protects the looped structure of nucleic acids.

Nuvec has been designed to deliver the cargo directly into the cells, and its properties have the potential to overcome many of the challenges of other approaches. The technology works by simply and effectively trapping and protecting nucleic acid (such as mRNA/pDNA) as it travels to the cells. It does not totally encapsulate the DNA or RNA, but rather binds and protects enough to deliver good transfection. The high surface area of the nanoparticle, due to the spikes, allows for high levels of material to be loaded onto the particle.

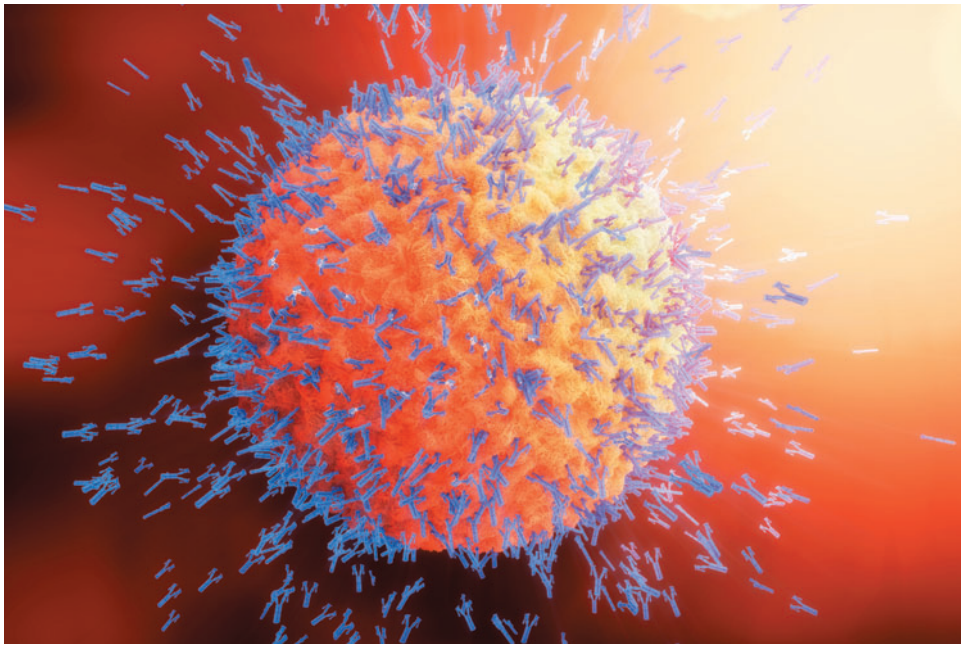
Once inside the cell, the cargo load is released to activate the immune system. Nuvec is also a natural adjuvant, so it attracts a large number of innate immune cells, which, in turn, leads to more activation of the adaptive immune system (T and B cells), thus increasing the level of immune response against the target cancer cells.

The Nuvec system offers the advantage of not posing unwanted systemic side-effects. Our data show that the trapped drug remains at the site of injection, doesn't produce unwanted inflammatory responses, and, very importantly, doesn't track to the liver. Nuvec is provided as PEI-loaded nanoparticles that can then have the relevant DNA or mRNA loaded onto them via a simple mixing process. The final drug product will involve the combination of the Nuvec particle with the DNA or mRNA itself. Nuvec is an intermediate step in the final drug product manufacture.

Andrade (Nanoform): At Nanoform, we have developed a technology called Controlled Expansion of Supercritical Solutions (CESS) to engineer API particles to the nanosized scale that will give failed drug candidates a second chance and enable more successful drug product development. CESS elevates particle engineering, and we focus on the generation of crystalline nanoparticles, typically with a Dv50 (i.e., median volume distribution) below 200 nm, directly from solution and with a high-yield (over 90%). We take any API and study its physical and chemical properties to define the process parameters to apply CESS to the molecules for which we want to generate nanoparticles. We start by preparing a suspension in carbon dioxide, turning it into a solution, and then controlling the nucleation step by controlled pressure and temperature drops that are coupled to a final atomization step. The process is used to obtain the crystalline nanoparticle dry powder. As it is a recrystallization step, Nanoform's technology is part of drug-substance manufacturing and can seamlessly be integrated into any drug product development supply chain. As Nanoform's technology does not require excipients or surfactants, the free-flowing nanoparticles generated are compatible with any drug product development strategy. We anticipate that our work will double the number of molecules that enter the market.

REFERENCES

1. S. S. Suri, H. Fenniri, and B. Sigh, *J Occup Med Toxicol.* 2 (16) (2007).
2. J. K. Patra et al., *Journal of Nanobiotechnology* 16 (71) (2018).
3. G. Parisa and M. Soliman, *Research in Pharmaceutical Sciences* 13 (4) (2018).
4. FDA, *Draft Guidance for Industry, Drug Products, Including Biological Products, that Contain Nanomaterials* (Rockville, MD, December 2017).
5. EMA, *Reflection Paper on Nanotechnology-Based Medicinal Products for Human Use*, June 2006, www.ema.europa.eu/en/documents/regulatory-procedural-guideline/reflection-paper-nanotechnology-based-medicinal-products-human-use_en.pdf.◆



Taking Therapeutic Antibodies to the Next Level

This article explores the challenges and potential of next-generation therapeutic antibodies.

FELIZA MIRASOL

Monoclonal antibodies (mAbs) are considered the standard therapy in the biologics industry following decades of research, development, manufacturing optimization, and commercial success. However, they face limitations to their long-term efficacy because they can eventually encounter resistance, such as when a tumor evades immune control (1). Fortunately, advances in protein engineering technology have led to the development of alternative antibody forms, or next-generation antibodies, that may supersede the limitations of mAbs. At the forefront of a new wave of next-gen antibodies are bispecific antibodies, which are capable of targeting multiple antigens as a single agent. Bispecific antibodies can directly target immune cells to a tumor, which suggests that they can significantly reduce drug resistance and severe adverse side effects commonly experienced with other cancer therapies, including mAbs (1).

ROAD TO NEXT-GEN ANTIBODIES

Over the past 20 years, antibody therapeutics have grown from nothing to a $120-billion market that is the fastest growing sector of therapeutics, says Carl Hansen, PhD, CEO and president of AbCellera, a Canadian biotech company specializing in next-generation therapeutic antibodies, and professor at the University of British Columbia, Vancouver, Canada. The biologics industry has since matured and has grown increasingly more competitive, driving a need for access to new target spaces and for new technologies that provide a competitive advantage, Hansen observes.

"On the one hand, the industry is moving towards target classes that have previously been inaccessible. At the same time, the competition amongst biotechs driving new antibody therapeutics to market has intensified. These market dynamics have placed a premium on high-end discovery technologies capable of finding rare antibodies, as well as access to new sources of antibody diversity that are suited to each specific problem," says Hansen.

For example, he notes, antibody discovery from camelids provides a means to generate high-affinity single-chain antibodies that can access small epitopes. There is also a trend toward the creation of formats in which a single molecule can engage two (bi-specific) or more (multi-specific) targets. Numerous bispecific formats have been described over the years; however, many of these have encountered challenges in manufacturing. More

Outsource to the Experts

Our assay kits provide the specificity and sensitivity to detect impurities with reproducibility that supports regulatory compliance.

Assay Kits

- Host Cell Protein ELISAs to detect and quantify HCPs from numerous bioproduction cell lines
- Protein A ELISAs to detect Protein A leachates from leading Protein A chromatography resins
- Bioprocess Impurity Assays to detect BSA, HSA, Transferrin, and Insulin
- Host Cell DNA Extraction and Detection Kits

Our advanced orthogonal analysis services identify impurities to help optimize downstream purification processes.

Contract Services

- Process-Specific Antibody and Assay Development
- Antibody Coverage Analysis
- Antibody Affinity Extraction (AAE)
- Comprehensive Assay Qualification
- HCP Analysis by Mass Spectrometry

Trust your assays. Trust your results.

cygnustechnologies.com

CYGNUS TECHNOLOGIES

part of **Maravai LifeSciences**

recently, these manufacturing challenges have been solved using protein engineering methods, and several bispecific molecules have advanced into the clinic, including immunoglobulin G (IgG)-like formats and nanobody molecules, which are truncated single-chain antibodies. The latter can be linked together to create constructs that are both simple to manufacture and that are capable of targeting more than one epitope or drug target at once, Hansen explains.

"Alternative scaffolds are a novel class of biologic molecules that have been specifically developed to address identified shortcomings of mAbs," adds Dr. Fredrik Frejd, chief scientific officer of Affibody, a Swedish biotech company specializing in next-generation biopharmaceuticals. "Alternative scaffolds are the focus of companies such as Affibody, Molecular Partners, and Pieris, and they feature on par molecular diversity and ability to bind with high affinity in a structure that is often better and very different from mAbs."

Alternative (aka, protein) scaffolds, which are derived from non-immunoglobulin proteins endowed with novel binding sites (2), are used to generate novel binding proteins via combinatorial engineering. They have recently emerged as a compelling alternative to natural or recombinant antibodies. The concept of this scaffold requires an "extraordinary stable protein architecture tolerating multiple substitutions or insertions at the primary structural level" (3).

Affibody has developed alternative-scaffold molecules, called Affibody molecules, that have shown substantial clinical usefulness in oncology and inflammation indications. The company currently has ongoing clinical trials with three different Affibody molecules in Phase II/Phase III for breast cancer imaging, Phase II for psoriasis, and Phase I for autoimmune diseases, respectively.

THERAPEUTIC POTENTIAL

Emerging antibody formats provide a variety of advantages, Hansen comments. Bispecific antibodies, for example, provide the ability to modulate multiple targets in a single molecule, to direct cell-cell interactions (T cell engagers), to increase target engagement on multiple epitopes, and to increase therapeutic windows by selectively targeting tissues or cell types.

Researchers have been able to take the modular architecture of antibodies and create more than 60 different bispecific antibody formats that vary in molecular weight, number of antigen-binding sites, spatial relationship between different binding sites, valency for each antigen, ability to support secondary immune functions, and pharmacokinetic half-life, according to a study by C. Spiess *et al.* (4). Having these diverse formats allows for tailoring the design of bispecifics to match a proposed mechanism of action and to serve an intended clinical application.

The Affibody molecules, meanwhile, offer therapeutic potential via their high molecular diversity and high stability as well as by demonstrating high affinity—down to femtomolar affinity—when binding to targets. "Higher subcutaneous doses due to smaller molecular size translate to greater clinical efficacy than antibodies, and the smaller size results in better tissue penetration and access to the disease target," says Frejd.

Alternative scaffolds offer improved manufacturability and can facilitate new functional combinations, which is likely to enable unique therapeutic modes of action that can yield promising therapeutics, such as biobetters (2). Affibody molecules, specifically, can be manufactured with predictable processes at low cost and offer engineering options not accessible for antibodies, according to Frejd.

CHALLENGES TO DEVELOPMENT

Next-gen therapeutic antibodies face many challenges, and bispecific antibody challenges in particular include the engineering, development, and manufacture of the molecules, says Hansen. "Much of the work on bispecifics has focused on solving the manufacturing problem of producing complex molecules with a single cell line with good purity and yield," he comments.

"AbCellera's platform is displacing discovery using traditional hybridoma or display approaches, two technologies that have changed little over the past two decades. Our microfluidic platform allows the direct assessment of antibodies produced by a single cell in hours and can be applied on a massively parallel scale to screen more than a million single cells per day. As compared to hybridoma methods, our process completely bypasses the need for a fusion step where the large majority of antibody leads are lost, thereby allowing an ultra-deep search of natural immune systems. By unlocking the full diversity of natural immune responses, we can produce large panels of naturally derived antibodies, which generally have superior potency, specificity, and developability as compared to those obtained from synthetic display libraries," Hansen adds.

In comparison, Affibody molecules offer biparatopic and multispecific constructs that can be generated at a fraction of the size and cost of an antibody, which allows for a switch from intravenous-infusion dosing regimes conducted in the clinic to a more convenient subcutaneous self-administration at home. "Typically, the production is scalable and predictable, and as the building blocks in the bi/multi specific constructs are synthetic, there are fewer surprises in the generation of the molecular formats. While two binding domains remain a limit for many antibody formats, tri- and multispecific constructs are routine with Affibody molecules," Frejd states.

REFERENCES

1. A. Thakur et al., *Blood Reviews* 32 (4) 339–347 (2018).
2. M. Gebauer and A. Skerra, "Alternative Protein Scaffolds as Novel Biotherapeutics," in *Biobetters*, A. Rosenberg and B. Demeule, Eds. (Springer, New York, NY, 2015), pp. 221–268.
3. P.A. Nygren and A. Skerra, *J Immunol Methods.* 290 (1–2) 3–28 (2004).
4. C. Spiess et al., *Molecular Immunology* 67 (2A) 95–106 (2015). ◆

pda.org/EU/Bio2019

2019 PDA EUROPE

BioManufacturing

3-4 SEPTEMBER 2019
MUNICH, GERMANY
EXHIBITION: 3-4 SEPTEMBER
IG MEETINGS 2+5 SEPTEMBER
TRAINING: 5-6 SEPTEMBER

REGISTER BEFORE 7 JULY AND SAVE UP TO €200!

CONNECTING PEOPLE SCIENCE AND REGULATION®

Streamlining Upstream Processing: A Good Place to Start

As cost and time pressures within biopharma are on the rise, innovative expression systems may offer companies a good opportunity to streamline processes early on.

FELICITY THOMAS

It is well-documented that biopharma companies are under increasing pressure to reduce timelines and costs associated with bringing a new biologic medicine to market. While some efforts to improve time and cost efficiencies have been made through single-use systems and novel production methods, such as continuous processing, there may be overlooked potential in innovative highly productive expression systems that could aid in the ultimate goal of bringing safe, effective biotherapies to market quicker and cheaper.

As reported by Allied Market Research, the global biopharmaceuticals market is anticipated to experience significant growth over the coming years, potentially reaching more than $500 billion by the year 2025 (1), with monoclonal antibodies (mAbs) expected to maintain dominance as the main type of product in commercial development. In terms of expression systems, mammalian-based expression systems (human-like) are used for most biologics, particularly for mAb bioprocesses, yet these are also attributed with relative high cost and low efficiency.

"Essentially, there are two key challenges currently facing the biopharma industry," says Abhijeet Kohli, product manager at Thermo Fisher Scientific. "When it comes to traditional mAb processes, overall timelines are constantly being challenged and there are continued calls for faster commercialization. Here, the traditional processing methods the industry follows are proving to be something of a bottleneck."

The second challenge for Kohli relates to the new types of biologics that are entering the pipeline. "The bispecific and trispecific molecules that are increasingly the focus of immuno-oncology efforts presents a further challenge for biopharma," he notes. "These molecules are much more complex than traditional biologics and consequently have lower titers, so there is a lot of room to optimize manufacturability, reproducibility, and stability."

CURRENT SYSTEMS: BENEFITS AND LIMITATIONS

The current "work horse" in expression systems for biopharma is the Chinese hamster ovary (CHO) mammalian cell line,

confirms Michael A. Cunningham, associate director, Upstream Manufacturing Sciences and Technology (MSAT), Life Sciences—Process Solutions, MilliporeSigma. "These expression systems most commonly rely on antibiotic or metabolic selection mechanisms to generate high-expressing cell clones."

Mark Emalfarb, chief executive officer of Dyadic International, emphasizes that there are limitations on specific expression needs encountered with all cell lines. "The greatest disadvantage of CHO, for example, is its low natural productivity and high cost of drug development on a gram-per-liter basis production," he says. "CHO also has a long production time line—41–54 days from pre-inoculum to production bioreactor and 14–21 days for fermentation process with complex expensive cell media and buffer requirements for cell viability. All this leads to an expensive cost of goods sold (COGS)."

Additionally, Emalfarb notes that with CHO cell lines there is a need for expensive virus inactivation, which must adhere to strict regulatory requirements. "Mammalian cells may harbor or become infected by viruses which could render all the previous work of no value, or even destroy the manufacturing facility's value," adds Terence Ryan, chief scientific officer of iBio.

A further potential disadvantage of conventional mammalian cell lines may present itself in the field of next-generation medicines, such as bi/multi-specific antibodies as well as gene and cell therapies, clarifies Dr. Fay Saunders, head of upstream mammalian cell culture, process development, at FUJIFILM Diosynth Biotechnologies, UK site. "Mammalian cells are still limited in their ability to be able to express more complex, non-natural 'designed' molecules."

Yet, CHO and other mammalian cell lines are capable of producing large, complex proteins with post-translational modifications (PTMs), which are similar to those produced in humans, Emalfarb stresses.

In addition to mammalian/CHO cell lines, bacterial, insect, and yeast systems, which according to Dr. Nicholas Holton, R&D manager at Leaf Expression Systems, all dominate the landscape of biologics production. "The use of plants for biologics production (plant molecular farming) has been around as a nascent field for many years but has historically been held back by significant underfunding as the industry instead focused on improving the safety profiles and yields of conventional systems," he says. "However, now that plant expression technology has finally matured and proven its commercial viability, it is increasingly being recognized as a valid commercially viable manufacturing option for diagnostic and therapeutic products."

Ryan also notes that plants can carry out most of the post-translational modifications exhibited by mammalian cells, and any additional mammalian-specific factors necessary for maturation of a biologic can be added with additional vectors. "Plants do not naturally exactly recapitulate human glycosylation (neither do rodent cells like CHO or myeloma), but this is generally not an issue, and modified plants with more human glycosylation capabilities can serve as hosts, and mAbs produced in plants have been shown to have more potency in antibody-dependent cell-mediated cytotoxicity (ADCC) assays than those made in CHO," he says. "Using stably-transformed plant cells (Protalix) has some of the time issues of mammalian cells due to the need to find just the right clone and coax it into performing in large bioreactors, but plant-manufactured proteins are well tolerated by humans and non-immunogenic in sustained administration."

"Bacterial cells, such as *E. coli* [*Escherichia coli*] cell lines, however, are unable to produce complex, mammalian-like glycosylation due to the absence of the necessary enzymatic components and the intracellular compartmentalization required," Ryan adds. Although, as he points out, bacteria offer a cheaper alternative to mammalian cell lines. "Insect systems can also be useful," Ryan continues, "but haven't really broken through (except for a flu vaccine) yet, and there is a potential risk in that baculoviruses can be taken up by mammalian cells, which is little appreciated."

A major disadvantage for yeast expression systems is the relatively low yield achieved when using these lines, explains Ronen Tchelet, Dyadic's chief scientific officer. "Yeast expression systems have a relatively low yield in comparison to the current CHO cell lines and the production of high mannose residues within the expressed PTMs (50–200 vs three molecules in human cells, as part of either N- or O-linked glycan structures)," he adds. "This change in the glycoform's structure may confer a short half-life and render proteins less efficacious and immunogenic in humans. C1 is head and shoulders above this cell type for the reasons noted above."

Higher titers are always desirable within the industry, but when titers are driven primarily by transgene copy numbers, there is a possibility that genetic loci can become unstable, which can lead to titers lowering during the manufacturing process, reveals Cunningham. "Furthermore, high titer processes that are driven predominantly by maximizing biomass can make downstream processing complex, impacting product quality."

LOOKING AT THE FORESEEABLE FUTURE

As has been discussed earlier, there is an increasing emphasis being placed upon speed and cost within biopharma, states Ryan. "At iBio, our technology obviates the need to spend months isolating a cell clone, allowing process development to begin within a month of knowing the target gene's sequence."

The cost and time pressures, which Holton notes are already considerable for the industry in terms of conventional expression systems, will only propagate with the advent of more personalized medicines as well as growth in the biologics and biosimilars markets. "Mammalian cell lines are slow to develop and expensive to scale into production. In the coming decade, a move towards rapid cheap and scalable expression technologies, which are capable of producing biologically active

human proteins, such as plant transient expression, will begin to attain a growing market share," he says. "The pharmaceutical sector is extremely conservative and risk averse, so these changes in production will likely not occur quickly."

Concurring with the speed and cost issues surrounding mammalian cell lines, particularly CHO, Emalfarb stresses that time should not be wasted by the industry thinking that CHO lines are a viable future option of choice for the industry as it moves into this next phase of more efficient, speedy, and cost saving bio-manufacturing. "CHO cells grow too slowly, they require an enormous amount of money and energy to feed with nutrients and expensive media to force the CHO cells to grow and produce relatively low levels of protein per day resulting in high capital and operational expenditure. All to get a mediocre gram per liter output. The COGS here don't make sense compared to our C1 fungal platform for example," he says.

For Cunningham, CHO-based mammalian cell expression systems will maintain dominance of the bioprocessing space, at least for the foreseeable future. "However, efforts will also continue to develop non-CHO expression systems, particularly to support vaccine and gene therapy applications," he adds. "I anticipate that, given the pressures to reduce biopharma costs, there will be continued research focused on increasing speed and reducing cost to clinic in order to accelerate the bench to bedside timeline."

The ability to continually manufacture a product rather than through batch processing, perfusion, is an area of interest, according to Kohli. "Perfusion, however, presents a number of challenges, particularly around how developers assess quality and titers on an ongoing basis and whether key quality indicators remain intact throughout the entire process," he notes. "Should products fall outside of quality parameters, for example, it's vital to have measures in place that will segregate material that does not meet these criteria."

"The processes of the future and those of today must rely on biomanufacturing techniques that are efficient, robust, and of high quality," confirms Saunders. "It is, therefore, imperative that the expression systems and processes of the future continue to effectively isolate and identify the very best cell lines and strains."

Additionally, Saunders emphasizes the point that despite considerable increases in titers being witnessed over recent years, there is still more work to be done in this area. "Difficult-to-express molecules are still expressed at considerably lower titers and improvements must be made in order to achieve suitable expression levels to make them commercially viable," she says.

To be able to express novel entities, Saunders believes that there is a need to move away from traditional cell line or strain development. "Therefore," she continues, "there will more than likely be a rational re-design of existing expression systems or efforts put into identifying novel systems."

STREAMLINING STARTS UPSTREAM

"Streamlining the whole biologics process certainly starts with upstream processes," states Natasha Lucki, product manager at Thermo Fisher Scientific. "Researchers want to improve and make the overall process more efficient to shorten timelines. The idea of getting to the market first will always be at the forefront of developers' minds, especially as new categories of biologics come into the pipeline."

According to Lucki as new technologies continue to enter the biopharma space, a focus for scientists and developers will be to take a holistic approach toward the product pipeline. "Developing processes that will facilitate not one, but the entire biologics production chain from upstream to downstream," she adds. "For biopharma companies, increasing efficiency and enabling greater output while keeping quality in mind are very important."

Matthew Jones, Dyadic's chief commercial officer, stresses that despite it being known that CHO cell lines are less time and cost-effective than alternative systems, there is a lethargic resistance to change by the industry. Risk adverse industries need pace setters that positively disrupt. "We need CEOs of biopharma to engage and look at the viable options for quicker and cheaper development of new biologic entities," he continues. "CHO cells grow slower, require expensive media to produce mediocre protein yields resulting in higher fixed and operating costs as well as expensive drug discovery processes."

Emalfarb goes further stating, "Modern advances in the use of synthetic biology technologies has come to cell lines. Alternatives, such as Dyadic's C1 fungal cell line, can offer more rapid growth at a lower cost, while producing higher amounts of protein per fermenter day. Not to move away from CHO to alternative lines is ignoring the incredible scientific breakthroughs and advances that are occurring faster in biopharma than Moore's Law did for tech."

For Ryan, biotherapeutics are at an interesting point with many novel and cutting-edge medicines under development in the laboratory. "Indeed, finding the sweet spot among several competing priorities—speed, cost of goods, biological activity, non-immunogenicity (except vaccines), and ease of purification—is important moving forward," he says. Therefore, other expression systems, such as iBio's transient plant expression system, may play an important role in transitioning these new products from the lab bench to the bedside of the patient, he asserts.

"The sector is under intense and growing pressure to increase R&D efficiency, to bring new drugs to market faster, and to manage costs more effectively," summarizes Holton. "While there is no silver bullet to address all these challenges, adopting highly efficient next-generation expression systems, such as plant-based systems can accelerate progress towards these goals."

REFERENCE

1. Allied Market Research, "Global Biopharmaceuticals Market: Opportunities and Forecasts, 2018–2025," *alliedmarketreseach.com*, Report (July 2018). ◆

Empowering HCP Identification with Antibody Affinity Extraction™ (AAE) and Mass Spectrometry

LIVE WEBCAST: Tuesday, June 18, 2019 at 11am EDT | 8am PDT | 4pm BST | 5pm CEST

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

EVENT OVERVIEW:

Host cell proteins (HCPs) are more than a check-off box on an investigational new drug or biologics license application. Knowledge of what HCPs are present can inform purification strategies to reduce the HCP level in drug substances. In this webcast, experts will discuss the integration of orthogonal methods for comprehensive HCP analysis, present data showing HCP identification by mass spectrometry (MS) before and after Antibody Affinity Extraction (AAE), and highlight how this information provides actionable insights into downstream process development and purification improvements.

Topics to be addressed include the following:

- Importance of detailed Information of HCP profile
- Antibody Affinity Extraction
- Role of mass spectrometry in HCP analysis
- Antibody Affinity Extraction and mass spectrometry case studies

Key Learning Objectives

- Learn why Antibody Affinity Extraction (AAE) is a superior alternative to 2D Western blotting for HCP antibody coverage analysis
- Understand how enrichment of HCPs by AAE and identification by mass spectrometry is a powerful alternative orthogonal method to enzyme-linked immunosorbent assay
- Learn how biopharmaceutical companies that integrate MS with ELISA data can provide comprehensive quality control data for regulatory agencies

For questions contact Martha Devia at MDevia@mmhgroup.com

Who Should Attend

- Bioprocessing scientists, process engineers, managers and directors

Presenter

Jared Isaac, PhD, MBA
Senior Scientist, Research and Development
Cygnus Technologies

Moderator

Rita Peters
Editorial Director
BioPharm International

Sponsored by

CYGNUS TECHNOLOGIES
part of Maravai LifeSciences

Presented by

BioPharm INTERNATIONAL

Addressing the Complex Nature of Downstream Processing with QbD

Quality by design brings both challenges and benefits to the development of downstream processes.

SUSAN HAIGNEY

Regulators have been encouraging bio/pharmaceutical companies to incorporate the concept of quality by design (QbD) into development and manufacturing processes for more than a decade. The International Council for Harmonization (ICH) defines QbD as a systematic approach that incorporates prior knowledge, results of studies using design of experiments (DoE), use of quality risk management, and use of knowledge management throughout a product's lifecycle (1). QbD incorporates the identification of critical quality attributes (CQAs) through a quality target product profile (QTPP). Critical material attributes (CMAs) and critical process parameters (CPPs) are identified through product design and understanding. Specifications for the drug substance, excipients, and drug product and controls for each manufacturing step are determined through a control strategy. The final elements of QbD are process capability and continual improvement (2). These steps combine to build quality into pharmaceutical processes and products over the lifecycle of a pharmaceutical product.

The industry has been slowly adopting the QbD approach, but with the boom in the biopharma industry, how have these QbD principles fit into the complex nature of biologics? According to Gunnar Malmquist, principle scientist, GE Healthcare, QbD has become an integral part of the development process for the biopharma industry. "We notice that the interest to file according to the QbD framework has cooled off during the past several years, but it is common during biopharmaceutical development to utilize and align with the principles of QbD as part of development activities. Nowadays, it is a structured methodology for how to approach product development that is not driven by regulatory need, but rather internal needs related to the establishment of process understanding," says Malmquist.

CHALLENGES OF QbD IN DOWNSTREAM PROCESSING

With the complex nature of biologics comes more complex quality concerns. Joey Studts, director late-stage downstream development in the bioprocessing development biologicals department at Boehringer Ingelheim (BI), notes that large-molecule products have more input

parameters that could possibly affect quality. "From my understanding, the number of input parameters that can have a significant impact on product quality is higher in the large-molecule world due to the multiple biologically based upstream unit operations and the complexity of assigned direct correlations," says Studts.

Therefore, using QbD to design downstream processes has its challenges. One challenge is the unpredictable relationships between molecular properties and downstream processes, but there is also the opportunity to concentrate efforts on the areas that are most important, says Malmquist. "Especially for novel molecular formats, one of the remaining challenges is the complex relationships between molecular properties and downstream processes," explains Malmquist. "In addition, the inherent high risk for drug failure at early stages of development combined with short development timelines suggests the need for a platform approach to manage the early phases of drug development and conduct more detailed characterization towards late-stage process development," he says.

To address this challenge, Malmquist recommends relying on process steps that are less risk exposed to avoid unpredictability. "For instance, protein A or affinity resins in general, as well as flow through steps, display these properties since these steps in most cases build on a fundamental understanding of the physiochemical phenomena involved in their performance," he says.

The removal of product-related impurities is another challenge, according to Malmquist. "In these instances, characterization of the interplay and impact of process parameters and raw material attributes is required to fully align with the QbD methodology, which translates into extended process development and characterization efforts. The effort can be reduced by a risk-based approach where the studies are focused on the most important (or less well-known) factors." To address this, the use of mechanistic modeling, and other emerging techniques, can reduce the experimental burden and concentrate efforts to attributes displaying the highest risks, Malmquist says.

> Use of mechanistic modeling can reduce the experimental burden and concentrate efforts to attributes displaying the highest risks.

"Typically, process parameters and their variability are well characterized, whereas the interplay between them and, for instance, resin variability may represent a blind spot," says Malmquist. The impact of variability regarding raw materials can be felt first in commercial manufacturing because of a lack of relevant test material during process characterization. "The only viable approach to become more proactive is to engage in a true partnership with the raw material suppliers to share knowledge, get access to relevant samples to develop a successful control strategy," he adds.

When it comes to early development, Doug MacDonald, senior scientist at Seattle Genetics, a biotech company that develops and commercializes cancer therapies, states that "speed to clinic" can inhibit the application of QbD. "Our typical IND [investigational new drug] timelines assume that the protein will fit the platform and therefore won't require a lot of additional development efforts. We have definitely seen therapeutic proteins becoming more complex and have had challenges at times with the downstream process. In one case, we had an engineered antibody, which possessed properties that were not entirely amenable to our platform purification process."

The company developed a new platform process for these types of proteins by doing a large amount of the work early on. "The knowledge we gained during that process will definitely help in the later potential scale-up and commercialization of the product; however, having more of a characterized operating space is not typical in the [Phase I] development process. It is important for QbD to link early and late-stage processes, and to address this we have changed our platform to be representative of the potential commercial process. We have also developed many high-throughput tools applicable to process and product development within upstream, downstream formulations, and analytical development," MacDonald says.

THE BENEFITS OF QBD IN DOWNSTREAM PROCESSING

When developing processes for downstream applications, companies are using QbD to develop and track goals and evaluate risk of development processes and steps. Seattle Genetics takes a holistic approach to downstream process development, according to MacDonald. "In early development, we leverage platform data to expedite the time to produce tox material test article and clinical material. However, for later stage and commercial, we employ detailed risk assessments based on FMEA [failure modes and effects analysis] concepts to guide the needed studies and scope

of work. These risk assessments are influenced by platform data, previous process characterization knowledge, available GMP data, and subject matter expertise. DoE activities are applied where appropriate models are generated to characterize the study space and possible impacts the process has on the product," says MacDonald.

QbD should also be used to document and track the progress of process development goals, according to Studts. "We use the therapeutic and clinical goals of the program as defined in the QTPP to execute a risk assessment of the quality attributes to clearly define the CQAs for the process and use these as a basis throughout development." Studts says CQAs, process performance, and other goals should be written in a development protocol document. Experiments should then be designed and executed so that relationships can be defined between input and output parameters.

QbD can be applied down to specific process levels as well, including the development of process materials. GE Healthcare uses QbD in the company's development of resins. "General Electric has for a long time used a Design for Six Sigma, which is built on the same principles as QbD. For resin development at GE, this means that external user needs are converted to functional properties that can be measured internally during resin development. These are matched to structural properties of the resin that plays the same role as quality attributes in QbD. These potentially critical resin characteristics are always studied together with chromatographic process parameters at relevant process conditions during our development to ensure productivity and robustness," says Malmquist.

Some downstream processes require more rigorous study than others, according to MacDonald. "Polishing steps such as ion exchange, hydroxyapatite, and hydrophobic interaction chromatography can be more heavily influenced by pH, conductivity, loading capacity, residence time, and temperature, and therefore would benefit more from a QbD approach. These steps are typically designed with more specific product attributes in mind and need more fine-tuning to achieve a goal of product or process related impurity or virus reduction," says MacDonald.

Operations that have the greatest impact on the quality target product profile get the most benefit out of QbD.

When platform data already exist, others may require less study, such as affinity chromatography steps, low-pH viral inactivation, and nanofiltration, says MacDonald. "There can always be a need to study these steps further, and the expectation is to do so at later-stage process characterization; however, the number of parameters requiring defined operating spaces may be reduced because of the nature/modality of the step. Nanofiltration is difficult and expensive to study since the designated CPP impact on a product CQA is the viral content, which can only be tested at approved CROs [contract research organizations]."

According to Malmquist, operations that have the greatest impact on the quality target product profile get the most benefit out of QbD. Understanding how the interplay between process parameters, raw material attributes, and the control strategy may affect CQAs could potentially reduce risk and improve development speed, says Malmquist.

"An example is the topic of product aggregates that can trigger immunogenic responses. It is therefore common to reduce aggregate content to below a threshold value using cation exchange, multimodal chromatography, or hydrophobic interaction chromatography. For this kind of step, it is important to understand the process parameters such as load ratio, buffer ranges, as well as resin ligand density when developing the control strategy," says Malmquist.

While Studts believes all process steps benefit from QbD, platform-based unit operations with previously established input and output parameters are not "actively developed with QbD principles."

"Process steps or unit operations where the quality attributes are impacted by input parameters within the step require product-specific data and therefore benefit from an active QbD approach. Regardless whether platform or product-specific parameters are used, each unit operation benefits from having a clearly defined target or target range for the unit operation. With output target ranges clearly defined, the variability of the input parameters is tested to define a proven acceptable range (PAR). This PAR is then compared to the uncontrollable variability of the input parameter or normal operating range (NOR). With these two input ranges set and considering the equipment capability around the input parameter, the risk of this parameter is assessed, and criticality assigned. The risk assessment and criticality assignment are then the basis for the control strategy," says Studts.

QbD IN VIRAL CLEARANCE

Viral clearance is connected to patient safety, according to Malmquist. During

Contin. on page 32

BioAccord™ SYSTEM **SERIES | PART II**

Improving Confidence and Productivity in Released Glycan Analysis for Biotherapeutic Development

LIVE WEBCAST: Wednesday, July 17, 2019 at 11am EDT | 8am PDT | 4pm BST | 5pm CEST

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

EVENT OVERVIEW:

Owing to the impact on drug efficacy and safety, glycosylation has long been recognized as a critical quality attribute that requires in-depth characterization and close monitoring throughout the product lifecycle of biotherapeutics. Glycosylation is generally assessed at a released glycan level using fluorescence (FLR) detection to overcome the challenges in structural complexity and broad concentration range. While sensitive optical detection alone often lacks the specificity needed for unequivocal glycan structural determination/assignment, orthogonal technologies, such as high-resolution mass spectrometry (HRMS), can provide additional structural information. These technologies, however, face great difficulty to deploy in process development and manufacturing environments due to instrumentation and analytical methodology complexity.

In this webcast, participants will learn about:

- An easy-to-use workflow developed on the compact and integrated LC-MS System that can be efficiently deployed across organizations
- An end-to-end streamlined workflow for released N-glycan analysis from sample preparation to liquid chromatography (LC)-FLR-MS analysis thru reporting
- Improved productivity and reproducibility with automated sample preparation
- Case studies demonstrating how the simplified analytical workflow transforms high quality LC/FLR/MS data into meaningful results for released N-glycan analysis

Presenter

Ximo Zhang
Senior Scientist,
Biopharmaceutical
Scientific Operations
Waters Corporation

Moderator

Laura Bush
Editorial Director
LCGC

Register for the whole series:

PART I: Transforming High Performance LC-MS Analysis in Biopharma: From Molecular Characterization to Attribute Monitoring
ON-DEMAND WEBCAST Aired May 16, 2019

PART III: Developing a Robust CQA Monitoring Method via Multi-Attribute Monitoring Principles for Therapeutic Monoclonal Antibody Development, Manufacturing, and Lifecycle Management
LIVE WEBCAST: Tuesday, September 10, 2019 at 11am EDT | 8am PDT | 4pm BST | 5pm CEST

Sponsored by

Waters
THE SCIENCE OF WHAT'S POSSIBLE.™

Presented by

LCGC BioPharm INTERNATIONAL

For questions contact Kristen Moore at KMoore@mmhgroup.com

STARKOVPHOTO - STOCK.ADOBE.COM

Comparing Facility Layout Options for Managing Business and Operating Risks

MARK F. WITCHER AND HARRY SILVER

ABSTRACT

The authors present a risk analysis of the impact of various business and operating risks on three facility layout strategies.

Efficiently and reliably manufacturing biopharmaceuticals requires controlling business and operating risks using enterprise control strategies (ECSs). ECSs are built using the three manufacturing enterprise elements—process, facility, and infrastructure (1). The facility element includes the facility's layout strategy. The layout can be used to decrease the likelihood of realizing both business risks associated with product development and manufacturing, and risks associated with operating sequences of process unit operations (UO) grouped into logical operating units (LOUs) necessary for manufacturing products. After defining the goals of all control strategies (CSs) and briefly describing an enterprise's control elements, this article compares the impact of several common facility layout strategies, including the multi-purpose facility (MPF) (2, 3), on managing important business and operating risks.

MANUFACTURING FACILITY DESIGNS

Facility design layout strategies used within the biopharmaceutical industry generally fall into three categories:

- Purpose built facility (PBF)—Layout is designed around the process equipment required to implement a well-defined UO/LOU sequence for a process or set of processes. Large-scale manufacturing facilities designed around fixed stainless-steel systems are PBFs. The PBF may also use some or all single-use technologies. However, when a PBF is designed, the process implementation is simultaneously integrated into the facility layout to achieve the desired efficiency, segregation, and operating flows. PBFs may have more than one production train. Multiproduct manufacturing is usually executed on a campaign basis within a single process train. Flexibility is limited to process formats included in the initial design. Adapting a PBF to new processes can be expensive or not feasible because of ongoing manufacturing requirements.
- Shared flexible space facility (SFSF)—Layout design is based on using large open spaces for either fixed or moveable single-use technology or stainless-steel equipment required for making one or more products. The layout commingles a large number of UOs for one or more processes and products in a flexible open ballroom configuration. Segregation may be limited to large LOUs such as upstream and downstream, or specialize activities such as bulk filling. Operations within large spaces are conducted by common personnel to achieve labor efficiencies. Multiproduct operation may or may not occur within shared spaces. The simple layout of the SFSF reduces capital investment requirements. Amgen's Singapore facility is an excellent example of the SFSF layout concepts (4).

Mark F. Witcher, PhD is a consultant, witchermf@aol.com.
Harry Silver is senior process/facility designer at Harry Silver Designs.

PEER-REVIEWED

Article submitted: Feb. 13, 2019
Article accepted: March 19, 2019

- Multi-purpose facility (MPF)—Facility layout, as shown in **Figure 1**, is based on a matrix of small non-dedicated, multifunctional operating areas accessed by primary and out corridors allowing both bi and unidirectional flow of materials, equipment, and personnel. Multiproduct manufacturing is accomplished by placing product dedicated LOUs using movable single-use technology or stainless-steel equipment within a variety of possible room configurations capable of operating the process (2, 3). Advantages of MPF are similar to the SFSF except the MPF is more complex due to the increase in the number of rooms, corridors, and other facility systems.

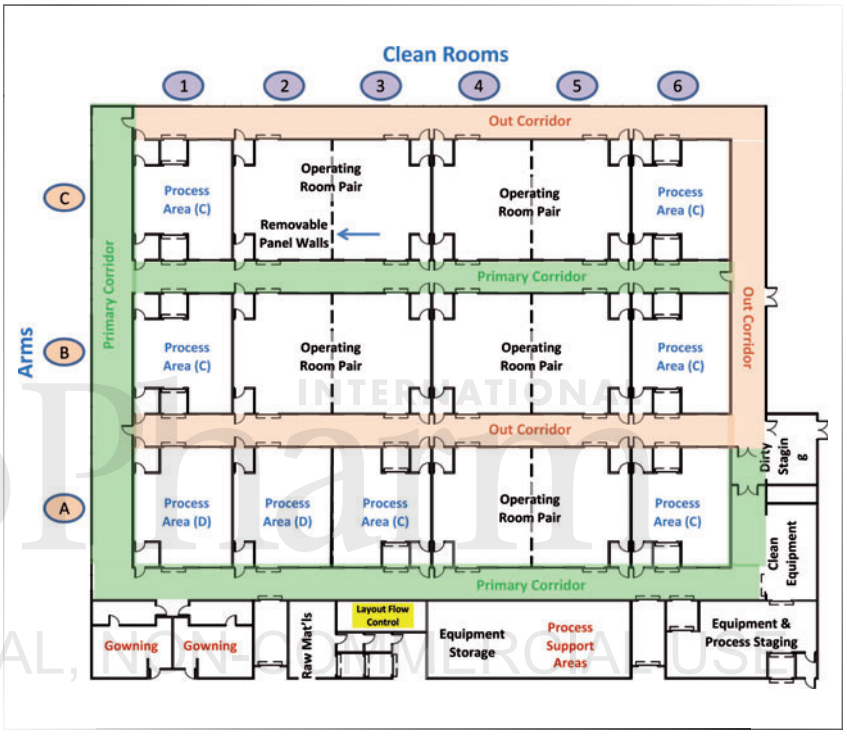
Each facility layout strategy has strengths and weakness. The PBF has been the classic layout strategy used to design biopharmaceutical facilities, particularly those for operating large stainless-steel systems for a well-defined process. The SFSF was developed using single-use technology to provide additional operating flexibility and reduce facility complexity to lower capital investment (4). The MPF was proposed to speed up the launching of new products by providing sufficient scale and process implementation flexibility to operate a wide variety of process formats and simultaneously support pre-clinical, clinical, and commercial manufacturing with minimal tech transfer time and effort (2, 3).

CONTROL STRATEGY GOALS

All manufacturing control strategies, including enterprise-wide control systems (ECSs) have three goals:

- State of control—Provide a qualified robust control strategy that reliably controls all the process's operating steps to achieve predefined product material attributes and process behavior quality metrics that assures each step can be released for executing the following operating step, including release of final product.

Figure 1. Matrix layout. Facility layout shown is a matrix of individual non-dedicated multi-purpose rooms in three arms (A–C) each having six rooms (1–6) that can be independently configured to house a variety of process and support function LOUs necessary to achieve the require manufacturing capabilities. All equipment, primarily single use, is movable for placement or relocation within the matrix as required to operate a wide variety of process implementations. The facility can be expanded by increasing the number of arms and the number of rooms in each arm in the initial design or adding arms later above the out corridor at the top of the figure (2, 3).

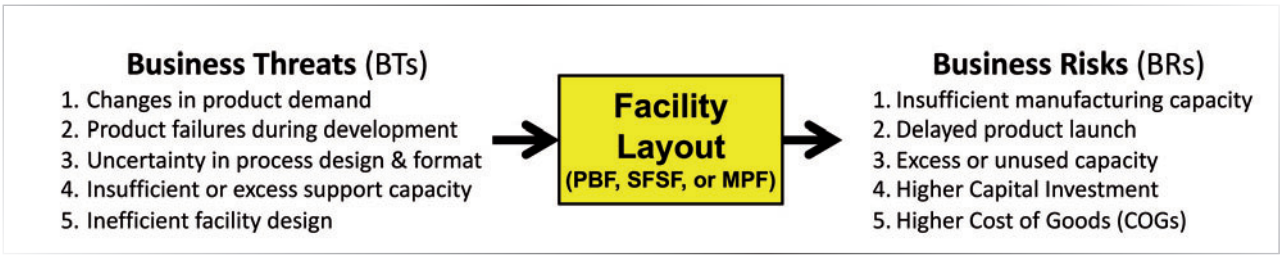


- Proof of control—Provide documented release based on product and process quality metrics at control points for each operating step to allow release for executing the next step. The information should be sufficient to prove to an unbiased external reviewer that the step was completed as planned and defined. Proof of control can be, by far, the hardest goal because it sometimes requires "proving a negative" associated with establishing that a failure of an external operation within the same manufacturing enterprise did not impact UO steps for other processes or products.
- Return to control—Should an operating step not pass its release criteria, assure sufficient process information is collected to determine the failure's impact on product quality and rapidly return the step to a state of control using an investigation, including a root cause analysis.

Achieving all three goals is a difficult task, particularly when dealing with multiproduct manufacturing of a wide range of upstream and downstream UOs combined into a variety of LOUs to achieve important operational and process segregation requirements (e.g., pre- vs. post-viral, etc.). Control strategies designed to achieve all three goals must be constructed using an efficient combination of the following ECS elements.

FIGURES ARE COURTESY OF AUTHORS.

Figure 2. Business risks (BR) and threats (BT) that may adversely impact the manufacturing enterprise. The discussion focuses on the relative likelihood of three facility layout strategies (PBF, SFSF, MPF) controlling the threat's ability to produce the risk consequences. PBF is purpose built facility. SFSF is shared flexible space facility. MPF is multi-purpose facility.



ELEMENTS OF ENTERPRISE CONTROL STRATEGIES

A pharmaceutical manufacturing enterprise can best be described by three elements that are combined to complement each other to achieve the above control strategy's goals. Each element provides important tools for building effective control strategies. The most efficient and effective ECSs use an appropriate balance of the following elements (1):

- Process—UOs, grouping of UOs into LOUs, process equipment, components, instruments, automated process control systems, input and in-process materials, and products. Process systems can include stainless-steel and single-use systems.
- Facility—Buildings, environmental systems, layouts, operational flows, logistical support, utility systems, and other building control systems such as the building management system.
- Infrastructure—Practices, procedures, people (training, discipline, and qualification), maintenance systems, and automated procedural control systems (MES, EBR, etc.) that control the facility and process elements.

The enterprise can be summarized as "the process operating inside the facility under the control of the infrastructure" (1).

With the control strategy's goals and the enterprise elements for building ECSs defined, the foundation of the risk management method for understanding the layout's impact on controlling various risks can be described.

RISK ANALYSIS APPROACH

The risk analysis approach is a system risk structure (SRS) methodology (5). SRS is based on a threat—process—risk consequence model shown in **Figure 2** for business risks and **Figure 3** for operating risks. SRS describes the likelihood that one or more threats, such as an input failure or change in the risk process, will result in a negative risk consequence (5). The risk process can be designed or redesigned to control the risk by decreasing the likelihood that the threat will successfully pass through the risk process to result in the realized risk.

A SRS's risk process can be anything from an entire manufacturing facility, in this case the facility's layout, to a simple piece of equipment or procedure depending on the scope of the risk analysis. Based on the processes to be evaluated, the risk processes can be combined into sequences similar to a process flow diagram (PFD) to form a SRS for analyzing complex risk problems (5, 6). Because all risks are assumed to be output consequences from a risk process caused by an input threat or trigger, the only difference between a threat and risk is the process it comes from in the PFD or SRS.

In this article, the risk process is limited to one of the facility layout strategies (PBF, SFSF, or MPF). If the facility layout does not control the risk by adequately mitigating the likelihood of the threat's impact, then the risk must be either accepted, or other ECS elements, such as scheduling, procedures, and facility modifications, must be added or enhanced as necessary to provide sufficient control of the threat. In the past, some of the business risks described in the following have frequently been accepted as a "fact of life" (e.g., product delays, shortages, additional capital costs, etc.) with great negative impact on patients and the business's bottom lines.

The following risk analysis subjectively rates the severity and likelihood of various threats and risk consequences relatively to each other. The subjective ratings are based on the author's 33 years of engineering, operations, and risk analysis experience in the biopharmaceutical industry (5, 6). When evaluating different layout options, each company should make the same ratings based on their specific situations, experience, and expertise.

SIGNIFICANT BUSINESS THREATS AND RISKS

The following discussion is limited to a few important representative threats and risks that could possibly occur to the manufacturing enterprise. **Figure 2** summarizes a few of the business threats (BT) and business risks (BR).

The threats are risk consequences that result from threat processes (e.g., from a prior or secondary threat) not described in this analysis. The

likelihood of the secondary threats occurring is assumed to be independent of the layout selected and thus outside of the scope of this discussion.

1. Changes in product demand (BT1)—Market forecasts have not accurately anticipated product demand.
2. Product failures during development (BT2)—Product fails during clinical testing and no longer needs to be manufactured.
3. Uncertainty in process design and format (BT3)—During process development, the UO/LOU sequence or format for a new product is significantly different than previous processes (e.g., from batch, used to design the facility's layout, to an intensified or continuous process).
4. Insufficient or excessive support resources (BT4)—Capacity limitations resulting from and inability to supply the process with sufficient media or buffers.
5. Inefficient facility layout (BT5)—The layout increases operating labor or capital investment.

Although the business threats vary widely between companies, their impact severity on patients and economic sustainability can be ranked qualitatively relatively to each other (> greater than, >> much greater than) in the following order: (BT1>BT2 >> BT3>BT4 > BT5).

Each of the layouts could be impacted by any of the threats individually or collectively to result in the risks described as follows. Each risk will be briefly discussed in terms of the layout's overall ability to decrease the likelihood of the threat's impact on producing the risk. A detail analysis is left to each company to understand the impact of the threats and risks on selecting a layout strategy.

The following BRs shown in **Figure 2** are subjectively evaluated without considering the interactions with the operating risks. Realization of operating risks can also have a significant impact on any or all of the following BRs:

1. Insufficient manufacturing capacity (BR1)—Demand for clinical or commercial material cannot be supplied because manufacturing capacity is unavailable or existing manufacturing capacity cannot run the required process.

Relative likelihood rating: BT1 >> BT3 > BT4.

Unless initially constructed (an exposure to BR3, BR4, and BR5), expansion of the PBF's capacity requires the time and capital for building a new facility or extensively modifying the existing layout. The SFSF can prioritize product campaigns, but rearranging processes in different configurations and formats (BT3) may be difficult to achieve without interfering with on-going manufacturing and increasing operating risks.
Because of its high flexibility, the MPF can quickly prioritize products to increase capacity or be quickly expanded by adding additional suite rows at the top of **Figure 1** with minimal impact to ongoing production.

Relative overall threat mitigation rating: MPF > SFSF >> PBF

2. Delayed product launch (BR2)—An inability to launch a product due to the unavailability of manufacturing capacity.

Relative likelihood rating: BT1 > BT3 > BT4.

Having capacity creation on the critical path can have a significant impact on the approval process, patient health, and business revenue. The impact of prebuilding capacity (BR3, BR4, BR5) is significant and depends on the flexibility of the facility to accommodate different processes associated with other products in the pipeline.

PBFs are typically not designed for scale flexibility or efficiently adaptable for both early clinic and commercial-scale process campaigns. Including options for scale and process flexibility significantly increases capital investment.
SFSFs may be designed with scale flexibility, but extensive infrastructure control strategies are required to manage commingled multiproduct pre-clinical, early clinical, and commercial production.
The segregated matrix of the MPF provides a great deal of process scale and format flexibility.

Relative overall risk mitigation rating: MPF > SFSF >> PBF

3. Excess or unused manufacturing capacity (BR3)—Unused manufacturing capacity because of BT1, BT2, BT3, and BT4. BR3 is concomitant with BR4 and BR5.

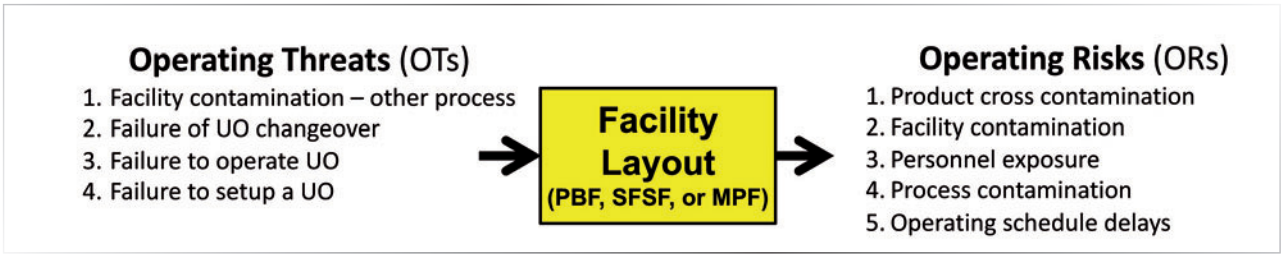
Relative likelihood rating: BT2 > BT1 >> BT3, BT4.

The PBF is the most likely to be oversized because it may have to accommodate future capacity growth associated with possible market expansion. Other products produced in the PBF would have to have similar processes.
The SFSF has some flexibility to manipulate its equipment arrangement to adapt to other product's processes, but product change-overs are more difficult during production of other products.
The MPF can quickly adapt to other products for clinical or commercial manufacturing regardless of scale and process format.

Relative overall threat mitigation rating: MPF > SFSF >> PBF

4. Higher capital investment (BR4)—Excess capital investment might result from building unneeded or unusable manufacturing capacity,

Figure 3. Operational threats and risks that may adversely impact the performance of the manufacturing enterprise. The discussion focuses on the relative likelihood of three facility layout strategies (PBF, SFSF, MPF) controlling the threat's ability to produce the risk consequences. UO is unit operations. PBF is purpose built facility. SFSF is shared flexible space facility. MPF is multipurpose facility.



including an inability to manufacture pre-clinical or early clinical products in the pipeline; concomitant with BR3. The risk of spending too much capital is largely dependent on the flexibility of the facility to adapt to the threats.

Relative likelihood rating: BT2 > BT1 > BT3.

If the PBF is designed for process and capacity flexibility to handle capacity uncertainty, capital costs increase significantly.

The SFSF's flexibility may be limited by ongoing manufacturing, and unanticipated process formats may be difficult to incorporate.

MPFs have significant flexibility and thus are more likely to be usable for manufacturing new products over their entire lifecycle.

Relative overall threat mitigation rating: MPF > SFSF >> PBF

5. Higher cost of goods (COG) (BR5)—Facility is inefficient and results in a higher cost of goods for making clinical and commercial products. This risk can be caused by threats BT1 and BT2; concomitant with BR3 and BR4.

Relative likelihood rating: BT2 > BT1 >> BT3, BT4 > BT5.

For a well-defined process with known capacity requirements, PBFs often can provide the lowest COG. However, COG may increase significantly as the uncertainty of the process definition and capacity requirements increase.

The SFSF can control costs by sharing operating labor within common areas allowing staff to work on multiple LOUs at the same time. However, COG may increase and operating flexibility may decrease due to control strategies additions required for operating commingled processes.

The COG advantage of the MPF relies on its flexibility to achieve a higher utilization rate under high uncertainty from being able to manufacturing many different clinical and commercial products using a wide range of different processes.

Relative overall threat mitigation rating: MPF > SFSF >> PBF

OPERATING THREATS AND RISKS

Operating risks are important secondary threats to business threats that may ultimately produce business and patient supply risks. The analysis of how operating risks threaten business risks is outside the scope of this analysis. The layout can have a significant impact on mitigating operating threats to prevent the likelihood of realizing operating risks shown in **Figure 3.**

The discussion here will be limited to the operating risks caused by the representative operating threats shown in **Figure 3**. To understand how the layout might control the threats to minimize or prevent the operating risks, the risk process is again the facility layout. For layouts that provide minimal threat control, other ECS elements such as closed single-use systems, procedural, and time-based sequencing controls must be used to minimize the likelihood of the threats producing one or more operating risks.

The operating threats (OTs) are the result of secondary threats to operating threat processes from equipment, components, procedures, and human operator errors used to operate the process and facility systems. In most enterprises, the largest source of secondary threats are mistakes by operating personnel (7, 8). In this analysis, the secondary threats are assumed to be independent of the layout. The following are the representative operating threats:

1. Facility contamination–other process (OT1)—Facility is contaminated from an external operation such as a second product in a multiproduct operation unrelated to the immediate process steps being evaluated.
2. Failure of UO changeover (OT2)—Failure to properly execute a lot or product changeout requiring clean-up and removal of single-use components or cleaning of a contaminated stainless-steel system.
3. Failure to operating UO (OT3)—A failure that occurs

during normal operation (e.g., a leaking bag or coupling or other equipment failure).

4. Failure to set-up UO (OT4)—A failure to properly setup a piece of equipment and prepare it for operation (e.g., incorrect connection or damaged single-use bag, etc.).

These threats, if realized, can result in the operating risks listed in **Figure 3**. Because of space limitation and incomplete knowledge of the processes, only the likelihood that the threat will result in a significant risk in the context of the facility's layout is discussed. For this analysis, secondary threats are assumed to be independent of the layout strategy. The operating risks (ORs) are:

1. Product cross contamination (OR1)—The risk consequence is an undetected or undetectable cross contamination of one product or lot with another product or lot.

Relative likelihood rating: OT2 >> OT3 > OT1.

The most important control objective is proof of control. The less segregated the facility's layout, the more reliance on closed single-use systems (a process ECS element) is required for preventing the risk. In general, single-use technologies are threatened by difficult to control human factors during setup, operation, and changeover. Controlling these secondary threats is difficult, but achievable by using both process and infrastructure (timing, procedures, training, etc.) ECS elements. The more UOs are commingled in a single space, the more complex the SRS making the ECSs to prevent both perceived and actual cross contamination more complex.

Relative threat impact likelihood rating: MPF > PBF >> SFSF

2. Facility contamination (OR2)—An equipment, procedural execution, or component failure, such as a leaking single-use bag that results in a contamination of the surrounding facility.

Relative likelihood rating: OT2 > OT3 >> OT4.

The extent of the process UO segregation plays a significant role in limiting the extent of the contamination's impact on other processes. The complex SRS of the SFSF makes controlling the impact of a facility contamination difficult. The complexity of the SRS is a key factor in designing a PBF and an intrinsic advantage of the MPF.

Relative threat impact likelihood rating: MPF >> PBF >> SFSF.

3.Personnel exposure (OR3)—Extent of exposure and ability to limit, isolate, and remove personnel from operating areas during a contamination event.

Relative likelihood rating: OT2 > OT3.

The high process segregation and unidirectional flow capability of the MPF is a significant advantage for isolating and mitigating personnel exposure in the event of OT2 and OT3. PBF and SFSF layouts may include additional controls in their design, particularly personal protection equipment.

Relative threat impact likelihood rating: MPF >> PBF>SFSF.

4.Process contamination (OR4)—Process UO becomes contaminated resulting in the loss of a lot (e.g., bioreactor contamination).

Relative likelihood rating: OT2 > OT1 >> OT3>OT4.

The likelihood of a process contamination is impacted by the number of threat interactions described by the SRS surrounding each UO. The more threat inputs to the UO, the more likely a contamination could occur (5).

Relative threat impact likelihood rating: MPF > PBF >> SFSF

5. Operating schedule delays (OR5)—Failure of one process causing delay of or interference with the operation of another process LOU. OR5 is typically not significant unless it causes a train wreck that impacts multiple processes and products.

Relative likelihood rating: OT2 > OT3 > OT1 >> OT4.

The more unit operations within a given space, the more procedural and scheduling controls will be required to prevent operational interference. The SFSF has the highest exposure to schedule "train wrecking" if operating threats occur at the wrong time in a large space executing numerous closely scheduled operations.

Relative threat impact likelihood rating: MPF > PBF >> SFSF.

CONCLUSION

The bottom line on manufacturing facility layout risks is the uncertainty factors that impact reliability and utilization. The above risk analysis evaluates the impact of various business and operating risks on the three facility layout strategies. If the manufacturing enterprise knows exactly what will be made over the facility's lifespan, the PBF with appropriate control strategies tailored to provide the defined process and capacity requirements is probably the most effective and efficient.

As the process and product uncertainties increase, the SFSF becomes more effective from its capital and operating cost advantages for multi-process operation. The higher

operating risks of the SFSF must be controlled by comprehensive infrastructure elements (scheduling, procedures, training, etc.) to mitigate a more complex SRS associated with the commingled processes.

When the process and product uncertainty become significant, the MPF has the advantage of the high process segregation that minimizes the SRS of the individual processes along with the MPF's ability to efficiently adapt its resources to a variety of different process formats and scales. The MPF has the additional advantage of controlling operating risks that allow the facility to support the entire product manufacturing lifecycle.

The choice between the PBF, SFSF, and MPF's layouts should be made by each company to optimize utilization and reliability depending on the anticipated threat and risk uncertainties of the product portfolio and the processes it anticipates needing to operate.

REFERENCES

1. M. F. Witcher, "Impact of Facility Layout on Developing and Validating Segregation Strategies in the Next Generation of Multi-product, Multi-phase Biopharmaceutical Manufacturing Facilities;" Supplement to *Pharm. Engr.* (Nov./Dec. 2013).
2. M. Witcher and H. Silver, *Pharmaceutical Technology* 42 (9) (2018), www.pharmtech.com/multi-purpose-biopharmaceutical-manufacturing-facilities-part-1-product-pipeline-manufacturing?pageID=1
3. M. Witcher and H. Silver, *Pharmaceutical Technology* 42 (11) (2018), www.pharmtech.com/multi-purpose-biopharmaceutical-manufacturing-facilities-part-ii-large-scale-production
4. B. Bader, "Multiproduct Madness–Flexible Manufacturing Facility, Case Study Amgen MOF," presentation at ISPE Biopharmaceutical Manufacturing Conference, San Francisco, CA, Dec. 4, 2017.
5. M.F. Witcher, *BioProcess J*, 16 (2017), https://doi.org/10.12665/J16OA. Witcher
6. Witcher, M. F., "Understanding and Analyzing the Uncertainty of Pharmaceutical Development and Manufacturing Execution Risks using a Prospective Causal Risk Model", Submitted to *BioProcess J*. 2019.
7. T. Muschara, *Risk Based Thinking–Managing the Uncertainty of Human Error in Operations*, Routledge (Taylor & Francis Group, 2018).
8. G. Peters and B. Peters, *Human Error–Causes and Control* (CRC Taylor & Francis, 2006). ◆

Downstream Processing — *Contin. from page 24*

downstream processing, virus inactivation, virus filtration, and chromatography steps are performed. Malmquist believes designing viral safety into processes from the beginning is of "high value … delaying the testing to comprise validation and at the same time reducing the risk for surprises at late-stage process development. This can be done through linking understanding of how viruses can be cleared at different process conditions, this information can be utilized across development projects and reduce team effort and increase speed," he says.

Platform knowledge may be used to design most viral clearance steps, and if the molecule is performing in acceptable ranges, a control strategy can be set from historical data, according to Studts. "BI sees the implementation of platform knowledge to define NORs and PARs as well as a control strategy as QbD. In such cases, a few optimally designed experiments are executed to understand the sensitivity of the specific molecule to the unit operation and the platform parameters being implemented, and a full DoE- based series of experiments are not necessary," says Studts.

When it comes to monoclonal antibodies, MacDonald says that viral clearance processes are "widely known and understood", with most platforms being developed for effective and orthogonal approaches for inactivating and removing viruses. "The A-Mab case study is a good example of supporting the platform approach to viral clearance (3). We are always mindful that as new data emerges, process development (PD) scientists may need to evolve their strategies. For a long time, people thought that high-pressure operation of nanofilters was considered 'worst-case'. In recent years, data have come out justifying the opposite. In response, we have started testing our lowest operating pressure as part of the viral clearance validation package. Pressure excursions, including what may happen during product recovery buffer flushes, have sometimes been shown to lead to viral break-through during validation studies. We have adopted a risk mitigation strategy in response: we no longer buffer flush our nanofilters to recover the remaining product, essentially taking a yield loss on the step to ensure a quality product. We feel that this approach specifically addresses QbD," MacDonald states.

CONCLUSION

Despite the complex nature of biologics, Studts believes that QbD can be applied effectively in the development of downstream processes. "With an effective data and knowledge management system and the appropriate processes and experience, the exercise can be straight-forward due to the large amounts of data that already exist on the structure-function relationships for classical large molecule drugs (e.g., monoclonal antibodies). However, more novel structures and platforms will require that the industry expand its knowledge for these types of molecules," says Studts.

REFERENCES

1. ICH, ICH Q8 R2, *Pharmaceutical Development* (ICH, August 2009).
2. L. X. Yu et al., *AAPS Journal* 16 (4) (July 2014), www.ncbi.nlm.nih.gov/pmc/articles/PMC4070262/
3. CMC Biotech Working Group, A-Mab Case Study, www.casss.org/page/286 ◆

From Data to Information

Making siloed data accessible across functions and to contract partners is the first step to facilitating continuous improvement and enabling use of artificial intelligence in manufacturing.

AGNES SHANLEY

Biopharmaceutical manufacturers have often described operations as data rich but information poor. While advanced analytics and sensors collect more data than ever before, much of it may not be used or shared with the operations that need it most to prevent lost batches and quality or compliance problems. The rise in outsourcing has only intensified the challenge.

IDC Health Insights surveyed 126 biopharmaceutical and pharmaceutical executives in the United States and the United Kingdom and found a significant gap between their need and their strategies for harnessing data (1). More than 98% of respondents said that cross-functional data access was important or very important to their business strategies, and 94% described the ability to apply advanced analytics and/or artificial intelligence the same way. Respondents believed that data access would be crucial to improving overall quality and productivity as well as the return on investment of their R&D investments.

However, 51% of those surveyed said that they did not have a clear strategy in place to help them reach either of those goals, citing regulatory uncertainty, budget prioritization, and the need for more action from functional operational groups. As Kevin Julian, senior managing director in Accenture's Life Sciences practice, the survey's sponsor, commented, "Important insights that could lead to the discovery, development, and delivery of promising new treatments are too often trapped within the functional silos of ... biotechnology companies" (2).

While some pharmaceutical manufacturers are still using paper-based record systems, a growing number are digitizing processes and making more data accessible in the right context. On a fundamental level, open control systems and a common data structure have helped allow this to happen, according to Rockwell Automation, resulting in distributed control systems (DCS) that enable integration using unmodified Ethernet, and allowing two-way communication between enterprise resource planning (ERP) and manufacturing execution systems (MES) (3).

Work is underway to improve collaboration in preclinical and quality labs, where good laboratory practices (GLPs), rather than good manufacturing practices (GMPs), drive operations (see **Sidebar**) Much progress is being made in the area of batch records, and expanding

Image courtesy of Apprentice.io

GLPs: Better data access needed to improve compliance

Like many crucial regulations, good laboratory practices (GLPs) were enacted in 1979 after FDA observers found serious problems in documentation, training, and data integrity at a number of US research labs (1). Decades later, regulators still find deficiencies in the way that some companies' labs approach data integrity, training, and standard operating procedures (SOPs).

Another major problem that can be traced to GLPs is reproducibility. According to the Global Biological Standards Institute (GBSI), 50% of published preclinical research cannot be reproduced, a problem that results in product development delays and wastes $28 billion/year in the US alone (2). Culprits were found to be biological reagents and reference materials, study data, and lab protocols.

A number of tools are being developed to help lab scientists capture and use more data, for example, LabStep, an interactive digital platform designed to help scientists get around some of the deficiencies of electronic lab notebooks (ELNs) and refer directly to protocols, SOPs, and other important data (3). LabTwin is introducing a new voice-activated lab assistant at BIO 2019 in Philadelphia in June. Combining artificial intelligence, voice recognition, and machine language, the hands-free device allows researchers to document steps taken and save explicit details that cannot currently be saved in ELNs (4).

Ultimately, compliance depends on following best practices. Stuart Jones, regulatory quality assurance professional in good laboratory practice (RQAP-GLP) and director of quality assurance at PPD Laboratories' Bioanalytical Laboratory shared recommendations with *BioPharm International*.

BioPharm: What are GLP's biggest challenges?

Jones: Because we work in such a regulated environment, a seemingly minor matter can have a significant impact on quality. As such, training is an important best practice, from the time of hire, to retraining when a deviation occurs. Annual refresher training as well as specific group remedial training also should be provided when needed. Meanwhile, the use of automated or electronic systems, such as ELNs, can be especially beneficial in maintaining the most accurate documentation.

BioPharm: How do you recommend that companies tackle training?

Jones: Initial training, especially with newer employees, can be done through reading, lecture, and/or some type of knowledge or learning assessment, but the best results occur when that theoretical work is followed up and supplemented by hands-on training. This is accomplished most effectively by teaming new employees with experienced staff using training goals established within a predetermined curriculum. Some measure of refresher training should be required on at least an annual basis and it should be consistent across all experience levels. Metrics generated around unplanned protocol and SOP deviations, as well as human error, should be used as indicators in determining the course and effectiveness of current training plans.

BioPharm: What best practices do you recommend to make data less siloed and more accessible to those who may need it (on cross functional teams?)

Jones: One of the best ways to establish a more cross-functional approach and enhance data accessibility is to use one system across all sites. If one across-the-board system is not a possibility, then the multiple systems must be able to work in tandem. Data portals and SharePoint sites also can be utilized to securely share information on a real-time basis.

BioPharm: Reproducibility is a major problem for preclinical research. Is that also the case for quality control labs? What best practices do you recommend?

Jones: We have found that, after research and development of the method by our scientists, it is important to involve the sample analysis team in performing some, if not all, of the validation experiments, with technical assistance provided, as needed, by the R&D scientists who developed the method. This approach allows for a shared collaboration between the research and production teams, and continues into sample analysis to ensure reproducible results from the developed and validated method. Best practices include following the proper bioanalytical method validation guidances, the bridging of critical reagents, analyst method qualification, and scientific expertise/knowledge of the assay, as well as the use of incurred sample reproducibility testing as one of the bioanalytical lab's means of proving the method can be reproduced.

References

1.H. Danan, *Pharmaceutical Technology* 15(6) (2003).
2. L.Freedman et al, *BioPharm International* 28(10) pp 14-21 (2015).
3. Lab Twin, "Voice Activated Laboratory Assistant to Launch at BIO 2019," Press Release, www. scrip.pharmaintelligence.informa.com/SC125243/LabTwin-Voice-Activated-Lab-Assistant-To-Launch-At-Bio
4. J. Gould, "How Technology Can Help Solve Science's Reproducibility Crisis," *nature.com*, April 25, 2019, www.nature.com/articles/d41586-019-01333-0#MOO.

—*Agnes Shanley*

connections between electronic lab notebooks, laboratory information management systems, MES, and ERP to increase access to information. Augmented reality offers one way to do this at the basic data recording and recovery level.

Although use of artificial intelligence is more advanced in clinical, discovery, and research applications, new platforms are targeting manufacturing.

In addition, according to Emerson Process Management's consultant Johan Zebib, quality review management and review by exception are being used with MES (4). Data historians can also be developed as a point of access, a concept that Eli Lilly has leveraged with its contract manufacturers in medical devices (5). Vendors are offering tools that make this task easier, with applications that use machine learning and other facets of artificial intelligence, allowing users to make connections between data points that might otherwise have seemed unrelated.

AUGMENTED BATCH RECORDS

Apprentice.io has developed augmented reality and database applications that allow users to get feedback as they perform their jobs and to compare equipment performance and different batch runs (6). Contract development and manufacturing organizations (CDMOs) are becoming a more important market for the technology, says CEO Angelo Stracquatanio, using it not only to share data, but for training and troubleshooting in real time. "There are so many silos within manufacturing, and data are not being leveraged at different levels," he says.

In 2019, the company has made improvements to its augmented reality products with augmented batch recordkeeping products that extend batch connectivity to laboratory information systems (LIMS) and electronic lab notebooks (ELNs), allowing inputs to be captured for every batch. Users can analyze process data to compare batch runs and implement continuous improvement programs and analyze specific runs to isolate deviations, Stracquatanio says, leaving an audit train of data that can be mined to decrease variability.

A growing number of CDMOs are using Apprentice.io's Tandem remote telepresence tool to collaborate with their clients. The Apprentice System also collects voice, picture, and other types of data to create a rich audit trail. "For example, for a single-use filter, one can scan its bar code. Users now know what filter that is and can create an audit trail for it … and put data together in real time, using a hierarchy of importance to present data in a way that doesn't overwhelm the user." says Stracquatanio.

ARTIFICIAL INTELLIGENCE

Machine learning and artificial intelligence are also moving into pharmaceutical manufacturing applications. The technology is farther along in clinical trials and in discovery. Accenture launched INTIENT in May 2019 to focus on discovery, clinical, and pharmacovigilance applications. Amgen has been working with Tata Consultancy Services on a Holistic Lab digital platform using Dassault Systemes' BIOVIA, for process development (7).

However, some vendors are focusing on pharmaceutical manufacturing. Quartic.ai, for example, has launched an AI-driven platform to provide feedback to operators and to monitor and improve processes (8). The platform, which includes a data engine, designed to extract data from DCS, quality management systems (QMS), and data historians, as well as a connector that allows disparate software systems to communicate with each other, was designed to be integrated into existing plants and equipment, but Quartic is also working with a pharma company to embed the platform into a new facility.

Once deployed, machine learning models could … predict potential failures … to trace the source of the failure down to an individual component.

Quartic.ai cofounder and CEO Rajiv Anand has an extensive automation and reliability background and previously worked at Emerson. The company's management team members all come from pharmaceutical and automation backgrounds. "We didn't want pharma users to feel that they needed to be coders or data scientists," says vice-president of life sciences Larry Taber

LEVELS OF DIGITAL MATURITY

The platform is geared to the fact that every potential user will have a different level of digital maturity, says Anand. Once legacy data sources have been connected, the artificial intelligence engine can be used to solve a specific problem (e.g., monitoring an asset's performance for deviations), he adds. Some clients are using it for complex predictive work (**Photo,** above, shows the platform in use at a biopharm facility).

The company has applied the platform in a number of situations, including an effort to monitor and improve fermentation yield in a highly variable process where all critical quality attributes were under control. Quartic extracted data and identified a few key batches, Anand explains, and then built an algorithm to study relationships between the batches, clarifying eight years' worth of data and fingerprinting each phase of the process. Ultimately previously unknown sources of variation were discovered. Work will now focus on learning more about them .

The company has also done work with predictive maintenance. Anand recalls one project designed to baseline the performance of an autoclave. The equipment was modeled and industrial Internet of Things (IIoT) sensors used to get additional vibrational and ultrasound information. Once deployed, machine learning models could then predict potential failures with the ability to trace the source of the failure down to an individual component (i.e., a damaged valve).

There are many other applications where artificial intelligence could be applied to pharmaceutical manufacturing operations, particularly in visualizing end-to-end processes. As data analyst Jonathan Lowe (9) found at one company, more than 100 quality events were being investigated at any one time, stretching staff capacity. A machine learning model was designed to predict which events would take the longest to resolve. The model predicted more than 85% of the severe delays weeks before they happened, allowing quality managers to prioritize tasks more equitably.

REFERENCES

1. Accenture, "The Case for Connectivity in the Life Sciences," Infographic, *accenture.com*, , May 22, 2019, www.accenture.com/_acnmedia/PDF-101/Accenture-INTIENT-Infographic-IDC.pdf.
2. Accenture, "Accenture Introduces Intient," Press Release, *accenture.com*, , May 16, 2019,www.newsroom.accenture.com/news/accenture-introduces-intient-an-innovative-platform-to-advance-the-discovery-development-and-delivery-of-patient-treatments.htm.
3. B. Sisk, "Analytics Informs Decisions in the Facility of the Future," a Rockwell automation white paper to be published in July 2019 on *pharmtech.com*.
4. J. Zebib, "Review by Exception: Connecting the Dots," an Emerson Process Management white paper to be published in July 2019 on *pharmtech.com*:
5. D. Berg et al., "Data Sharing in a Contract Manufacturing Environment," a presentation at the OSI Soft Users Conference, 2017, *osisoft.com*, www.cdn.osisoft.com/osi/presentations/2017-uc-sanfrancisco/UC17NA02LS04_EliLillyBGoldingerAPadillaDBergCMoore_Data Sharingina Contract Manufacturing Environment_fordistribution.pdf?_ga=2.254688200.1912970547.158360174-1538190911.1557339846
6. A. Shanley, "Mixed Reality Gains a Foothold in the Lab," *Biopharm Lab Best Practices ebook* issue 2, pp 8-9, *pharmtech.com*, November 15, 2018, www.pharmtech.com/mixed-reality-gains-foothold-lab
7. A. Louie, "Empowering 21st Century Science in Life Sciences," an IDC Perspectives Paper, Document VS43749317, *idc.com*, May 2018, www.idc.com/getdoc.jsp?containerId=US43749317
8. F. Marizol, "Quartic Introduces AI Platform for Process Manufacturing Operations at INTERPHEX 2019, *biopharminternational.com*, www.biopharminternational.com/quarticai-introduces-ai-platform-process-manufacturing-operations-interphex-2019
9. J W. Lowe, "Why Biopharma Manufacturing Needs to Leverage Network Optimization Techniques via Data Science," *medium.com*, June 19, 2018, www.medium.com/bcggamma/why-biopharma-manufacturing-needs-to-leverage-network-optimization-techniques-via-data-science-ffe6e1bb5ee3 ◆

Image courtesy of Quartic.ai

Moving PAT from Concept to Reality

The learning curve for process analytical technology has slowed widespread adoption.

CYNTHIA A. CHALLENER

Process analytical technology (PAT) is applied in the biopharmaceutical industry for analysis of raw materials, in-process monitoring, and final product analysis. PAT is not only enabling, but essential, to continuous bioprocessing. With sufficient advances, emerging PAT solutions should ultimately make real-time release testing possible.

IN-LINE, AT-LINE, AND ON-LINE

To understand the state of PAT technology development, it is necessary to understand the different types of PAT operations used in biologics manufacturing. In-line sensors are placed in a process vessel or process stream to conduct the analysis *in-situ*. On-line sensors are connected to process side streams and perform periodic automatic sampling, returning fluid back to the process streams after analysis is complete. At-line—or off-line—analyses involve collection of a sample from the process, with analysis performed away from the process. In-line and on-line sensors allow for continuous process measurement and control, while at-line measurements cause a delay between sampling and availability of the results, preventing their use for direct process control.

STILL ON THE LEARNING CURVE

The biopharmaceutical industry and regulatory agencies have recognized the value of PAT. Although many large multinational manufacturers have adopted and implemented various forms of PAT, many companies are still struggling to get started, according to Joe Makowiecki, enterprise solution architect with GE Healthcare.

"Despite the fact that the concept is supported by most scientists, implementation is limited at commercial manufacturing sites. Adoption of PAT is certainly not progressing as fast as was expected 16 years ago," asserts Moheb M. Nasr, principal consultant with Nasr Pharma Regulatory Consulting. "While we [have seen] an increase in the interest in and value perception of PAT among our customers within the last two to five years, we believe that its full potential is not yet being used," agrees Svea Grieb, product manager for PAT at Sartorius Stedim Biotech.

In many cases, Makowiecki adds, reliable, low cost, on-line/at-line analytical sensors needed for the measurement of

CYNTHIA A. CHALLENER, PHD, is a contributing editor to *BioPharm International*.

critical product quality attributes and product-related species are not commercially available. An additional challenge is the development of sensor/detector/measuring technologies that allow for PAT in the single-use space.

For companies that have adopted PAT, these tools are applied for raw material analysis and monitoring/control of process performance, according to Arpan Mukherjee, technical committee coordinator for the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL). Raw-material characterization is performed using handheld Raman/near infrared (NIR) scanners. In bioreactors, in-line sensors measure pH, temperature, dissolved oxygen (DO), and carbon dioxide; in-line optical sensors (Raman, NIR) are coupled with multivariate modeling to measure metabolites. In addition, a variety of on-line tools measure cell density (dielectric spectroscopy, fluorescence spectroscopy); protein aggregates (size-exclusion chromatography and ultra-high-performance liquid chromatography [UHPLC]); product concentration (HPLC); and protein charge variants (ion exchange chromatography). Numerous at-line analyses evaluate host cell proteins (HCPs), DNA, viable cell density, bioburden, aggregates, product concentration, and particulates.

One of the greatest difficulties with many current at-line methods is the extended length of time required to receive results—for instance, 28 days for most cell-based assays. The focus of research in these areas is the development of rapid methods that are sufficiently accurate and robust to allow adoption.

UPSTREAM FOCUS

Most PAT tools that find wide use today are designed for application in upstream processes. "This focus is in large part due to the fact that initial protein quality and effectiveness are established during cell culture or fermentation. Changes in the bioreactor conditions during protein production will impact all downstream processes. In addition, the largest number of sensor technologies available for use in biologics manufacturing are designed for upstream applications," says Richard D. Braatz, Edwin R. Gilliland professor at the Massachusetts Institute of Technology (MIT). "Trace metals, glucose, lactate, pH, DO, amino acid content, glycosylation profiles, and HCPs must be measured to monitor the process and enable feedback/feedforward control to optimize yield (in-line and on-line only for control)," Mukherjee observes.

The challenge with downstream unit operations is partly the lack of obvious opportunities for using sensors, Braatz notes. In column chromatography, for instance, analysis cannot be performed until after the column, preventing any in-process monitoring. The diversity of downstream processes is also a consideration. "Not only are there many possible downstream unit operations, but also the critical quality attribute (CQA) most impacted by each step is diverse. The traditional methods for quality attribute measurement are also often product-specific," says Makowiecki. As a result, the diversity of downstream processing design makes it difficult to develop a universal set of technologies that will cover all of downstream processing for all molecules and their associated quality metrics.

Next-generation therapies are creating additional opportunities for PAT adoption, though. In personalized medicines such as autologous cell therapies, for instance, the nature of the treatment demands a process that is flexible and can dynamically adjust to wide variations in starting material, according to Grieb. PAT can account for the variations and peculiarities of the cells from different patients in an automated fashion, enabling a high process consistency irrespective of the starting material.

PAT can also help overcome the analytical challenges presented by viral vectors for novel vaccines and gene therapies. These products are not well-characterized molecules like monoclonal antibodies, but a complex of various proteins, DNA/RNA, and in some cases lipid membranes. "This complexity makes it hard to identify and understand the factors influencing the product CQAs. Hence, these processes benefit from a stricter control strategy, where high levels of automation and implementation of PAT and advanced data analytics play a key role," Grieb asserts.

ESSENTIAL FOR CONTINUOUS MANUFACTURING

Process intensification/continuous bioprocessing is a hot topic in the biopharma industry at the moment because it enables increased productivity of single-use facilities while decreasing the footprint. It also brings incentives to invest in PAT, and advances in sensor technology/connectivity will make continuous processing possible, according Makowiecki.

Intensified processes are much more complex than conventional fed-batch processes and therefore require tighter monitoring and control, adds Grieb. "PAT and automation do not only provide this, but also reduce the complexity for the operator," she says. In Nasr's view, PAT is critical for achieving the enhanced controls required to ensure quality throughout the entire batch during operation of continuous processes. "Regulators expect process monitoring and controls based on the entire batch data and the ability to revise controls to compensate for raw material variability or the use of different batches of raw materials," he observes. In addition to in-line process control, there is also a need for advanced in-line PAT for continuous/hybrid batch manufacturing to enable real-time batch release, according to Mukherjee.

MANY DRIVERS FOR ADDITIONAL DEVELOPMENT

One of the biggest advantages to using PAT and biopharmaceutical manufacturing is the increased process understanding that is gained, which leads to more consistent product quality, according to Ruben Carbonell, chief technology officer for NIIMBL. It also allows for increased productivity, connectivity, and automation, says Makowiecki. Reducing the need for manual sampling lowers the risk of operator error and contamination, while the timely identification and correction of process irregularities will help minimize the risk of lost batches, Grieb notes.

Furthermore, asserts Grieb, a well-characterized and monitored process together with scalable hardware can significantly reduce the cost and efforts of process scale-up and scale-down. Overall, therefore, PAT contributes to acceleration of process development timelines for reduced time to market, concludes Carbonell.

PAT should also ultimately make real-time product release possible. "PAT is bringing quality control testing closer to the manufacturing floor for on-time/real-time release and development of predictive models to enable active process control and reduce batch rejection rates," Makowiecki asserts. "Real-time release is important for reducing the time to market. Instead of sitting on a shelf in storage for up to several months, medicines can be put in the hands of patients very quickly if real-time release is possible," Braatz states.

Speeding drug development is crucial given that many drugs in clinical trials fail to reach the market. Drug companies would like to start manufacturing process development later in the overall development cycle—preferably during Phase III of clinical trials—in order to focus their investments on candidates that have the greatest likelihood of obtaining regulatory approval. By reducing process development timelines, PAT is making it possible for companies to take this approach, which saves time, money, and effort, according to Braatz.

On a similar note, advanced PAT solutions often serve as better methods for advanced process development. They allow for monitoring of processes and product attributes that can provide the most optimal candidates to take forward in terms of quality attributes and productivity, according to Stacy L. Springs, executive director of the Biomanufacturing Program at MIT.

> The diversity of downstream processing design makes it difficult to develop a universal set of technologies that will cover all downstream processing for all molecules.

Braatz adds that PAT provides increased production flexibility. "There is a lot of uncertainty about the market size when drugs are in development; the actual demand will depend on whether a drug reaches the market first before other competitors and how accurate predictions of the user base are. The more information that a company has about its processes, the better decisions it can make, such as about whether to scale up in single-use or stainless-steel equipment," he explains.

BUT BARRIERS TO ADOPTION REMAIN

While PAT implementation affords many benefits, there also exist many hurdles that must be overcome before it becomes widely adopted across the biopharmaceutical industry. Cost is certainly an issue. So is the lack of experience and experts with training in advanced analytics and modeling, according to Nasr.

There are regulatory challenges as well, says Grieb. "Some concepts of modern automation technologies and sensor technologies are not yet covered by regulatory guidelines, particularly those used for multivariate data analysis, which takes all available data and integrates them into a fingerprint. The adoption of such batch-fingerprinting concepts must be considered by the regulatory bodies." The same questions arise for multi-analyte sensors that are based on computational models, which is the case for spectroscopy, for example, she adds. The risk of delay to a filing application can result in the lack of a business case, according to Carbonell. The complex regulatory framework around the world also creates risk aversion.

Certain information technology questions remain, too, Grieb notes. A comprehensive automation strategy for an entire bioprocess, and potentially an entire production site, requires connectivity of all components and a centralized control unit. "That would require data sharing and access that implies safety risks. We experience reluctance among our customers to adopt new technologies such as cloud computing and wireless communication of PAT components," she explains.

On a more basic level, Carbonell adds that there is often lack of confidence in testing robustness and integrity testing. In addition, lack of thorough process understanding can lead to ambiguity regarding the attributes that should be measured. This barrier is readily evident with

the lack of integration into the existing process equipment installed base, automation platforms, and control strategies, adds Makowiecki. He also comments that the ability to identify the right opportunities to implement PAT without causing commercialization delays or rework, the need to design in PAT solutions through process development stages, and to really validate them during scale-up prevents adoption.

For continuous bioprocessing in particular, the lack of experience with PAT at commercial sites that have typically performed batch processing combined with the perceived business and regulatory risks of implementing new technologies are hindering PAT implementation, according to Nasr. "The lack of availability and reliability of cost-effective in-line/on-line analytical sensors needed for the measurement of CQAs and product-related species is one of the gaps in continuous processing, but with many companies evaluating continuous processing, there is also synergy to explore PAT as an enabler," adds Makowiecki. Sartorius also thinks intensified/continuous processing will boost novel PAT solutions, because as companies establish new manufacturing pipelines with unique requirements, they can justify the costs and efforts of going through the approval for commercial manufacturing.

TECHNOLOGY GAPS TO BE ADDRESSED

Overall, there needs to be a standard path to implementation for PAT, with technology available that fits each application and does so across all manufacturing scales and a practical approach to connectivity, according to Makowiecki. A higher degree of automation for upstream bioprocesses and standardization of the process steps would lead to improved batch-to-batch consistency, and in turn, product quality, Grieb agrees.

Grieb also notes that, while most PAT implementation has targeted upstream processes, there are plenty of examples where PAT could significantly improve downstream processes as well. Examples are automated venting of filters and protein quantification during column loading. "We expect to see more downstream targeted PAT implementation within the next years," she says. In particular, Springs points to a need for low-cost, robust, downstream PAT solutions that are non-invasive and do not require advanced interfaces with equipment, which can impact sterility.

There are also specific sensor technologies that need improvement or have yet to be developed, according to Kelvin Lee, NIIMBL's director. Examples include high-resolution, specific, robust PAT tools with a low limit of detection and in-line, reusable sensors with high frequency measurements that do not require calibration over the course of the batch. The ability to characterize proteins in a bioreactor on-line via a reliable, reproducible, rugged, high-precision, and high-throughput liquid chromatography–mass spectrometry (LC–MS) instrument at a cost of $300,000 rather than $1.3 million would be a game-changer, asserts Braatz.

Although a difficult problem to solve, sensors that rapidly measure viral and microbial contamination are needed the most, Braatz states. The long (28-day) time to receive results from cell-culture-based sterility tests could delay product release when needed, especially for vaccines or autologous cell therapies like chimeric antigen receptor (CAR) T. That is why application of rapid methods and next-generation sequencing for sterility testing is creating so much excitement, adds Springs. As importantly, if contamination is caught sooner using in-process rapid testing for virus or microbes, contamination can be stopped before spreading downstream in the process, saving both money and time.

EMERGING TECH IS EXCITING

Many PAT technologies are under development in both academia and industry. Braatz and collaborators at MIT and Biogen conducted an 18-month study to identify different technologies in use and in development for a wide range of CQAs and classified them according to the timeframe in which they were likely to be adopted (1).

Some of the promising emerging PAT solutions include slanted nano-arrays and spectral analysis with partial least squares for protein aggregates; microfluidic technology for analysis of post-translational modifications and sequence variants; nanotechnology-based analysis of charge heterogeneity that does not require protein purification; aptamer-based biosensors for N-glycosylation evaluation; next-generation sequencing (NGS) for viral and microbial contamination quantification; surface plasmon resonance, amplified luminescent proximity homogeneous assay, and fluorescence resonance energy transfer for target and Fc binding analysis; liquid chromatography coupled with ultraviolet, fluorescence, or MS detectors for evaluation of process-related impurities; and variable pathlength spectroscopy solutions for protein concentration measurement in real time (1).

Microfluidic devices and contact-free PAT technologies are among the most recent advances but are still mostly in the laboratory proof-of-concept stages, according to Carbonell. "Microfluidics-based analyzers require a small sample volume and provide higher resolution than existing PAT technologies," he explains. He points to three additional microfluidics technologies—particle analyzers for on-line protein aggregation detection and monitoring, devices for on-line or at-line detection of adventitious agents, capillary electrophoresis and

capillary isoelectric focusing-based microfluidics devices for real-time protein analytics—and MS-integrated microfluidics.

"These technologies are currently being evaluated by the biopharma industry and are in different phases of development (alpha and beta testing). They have the potential of increasing process/product knowledge, early detection of contaminants, and reducing the need for comprehensive endpoint quality testing," Carbonell says.

Spectroscopic methods (both Raman and NIR) are currently deployed but are not yet widely adopted, according to Makowiecki. Sartorius Stedim Biotech also believes that spectroscopic techniques will become more abundant in both upstream and downstream bioprocessing, due to its capability of label-free, online measurements of several analytes, cell properties, and product quality attributes. "Spectroscopy has the potential to replace offline measurements during the bioprocess. We envision the use of a combination of different spectroscopic techniques—such as NIR, Raman, and UV-Vis—to be required for this," says Grieb.

Soft sensing (transforming existing signals and leveraging advanced process understanding to infer/gain visibility to an attribute without direct measurement) is making it possible to monitor/predict performance through use of surrogates, according to Makowiecki. "As a result, the industry doesn't have to wait for sensor maturity for CQAs to begin their PAT journey," he says.

COMMERCIAL IMPACTS

The application of sophisticated PAT tools in combination with multivariate data analytics is starting to have a high impact on commercial processing, according to Grieb. "Measurements are moving forward in the process to the point of controllability. Using process fingerprints, the state of the process can be assessed at any time. Furthermore, through real-time univariate and multivariate process monitoring, data can be used for simulation and modeling of process design and control and ultimately lead to prescriptive analytics for product quality," she explains. In the near future, Sartorius Stedim Biotech also expects wider spread adoption of analytics in GMP that are already available, such as spectroscopy for metabolite control and bio-capacitance for viable biomass.

A standard path to implementation for PAT—with technology that fits each application and across all manufacturing scales—is needed.

Braatz is looking forward when cost of LC–MS systems is reduced sufficiently to allow widespread adoption for real-time monitoring of bioprocesses. He notes that few people in the 1980s would have expected powerful, easy-to-use, small-sized LC–MS systems to be hundreds of thousands of dollars, so development is on the right trajectory. NGS technologies are also very promising. "Next-generation sequencing could be very helpful as it is applied to more advanced and complex therapies, such as genome-edited products," Springs asserts.

Springs adds that some of the technologies being developed to measure the sterility of autologous cell therapies should be applicable to traditional biologics. "We may see more innovation in the cell-therapy space first," she says.

Overall, Braatz believes that PAT development has reached a point where there have been sufficient advances that have resulted in real improvements in analytical capabilities that the concept of real-time-release testing can be realistically considered. "We are getting to a very exciting place now," he says.

COLLABORATION IS NEEDED

Increased adoption of PAT will be driven by regulatory clarity and support, industry collaboration, advancements in connectivity and technology, the introduction of PAT-focused platforms and services by vendors, and further implementation of continuous processing, according to Makowiecki.

Emerging technologies are promising, but appropriate software and hardware development is necessary for integration into existing bioprocesses and for automation, especially for continuous/semi-continuous processes, notes Lee. "The coupling of these technologies with new automation systems is likely to dominate the future of biopharmaceutical manufacturing. A key challenge is the need to de-risk the adoption and implementation of these technologies in a highly regulated environment. We believe that public-private partnerships that enable multiple stakeholders to innovate collaboratively provide the opportunity to de-risk such advances," he states.

"It is essential to reduce the technical risk of emerging PAT solutions, especially as the industry moves toward real-time feedback control and scales out the manufacturing of autologous cell therapy products," according to Springs. "By working together, we can find the best solutions that allow medicines to get to the patients faster," she concludes.

REFERENCE

1. M. Jiang, et. al., *Biotechnology and Bioengineering*, 114 (11) 2445–2456 (2017). ◆

On the Right Track

Proactive approaches that consider long-term supply chain security compliance are recommended to ensure companies stay on the right track.

FELICITY THOMAS

Despite there being various terms used, counterfeit, falsified, fake, and so on, a drug that has been fraudulently manufactured and distributed to mimic an authorized medicine, whether branded or generic, poses significant risks to companies and, more importantly, to patient health. The World Health Organization (WHO) estimates that one in 10 medical products are substandard or falsified in low- to middle-income countries, based on a literature review of previously published papers (1).

In financial terms, as reported by Strategy&, PricewaterhouseCoopers' strategy consulting business, falsified medicines represent a lucrative proportion of illicit goods sold within the global market, estimated to range from €150 billion to €200 billion (US$163 billion to $217 billion) per year (2). Given the size of the market and the risk to patient health, many authorities have been implementing regulations to protect the security of the supply chain.

"The proliferation of online pharmacies, and the Internet in general, has meant that the pharmaceutical black-market has trickled into mainstream society and consequently become a widespread issue," asserts Staffan Widengren, director corporate projects, Recipharm. "As a result, health regulators have established new legislation and surveillance strategies around supply chains in a bid to prevent and minimize the circulation of falsified drugs. Without supply chain security measures, we cannot effectively track or determine the legitimacy of a drug product."

"Supply chain security is a core end-to-end capability in a business to ensure that all products reaching the patient are safe, compliant, and delivered on time and in full," adds Roddy Martin, chief digital strategist, TraceLink. "Most importantly, the elements of risk and security are proactively tracked across the end-to-end business so that any deviations are detected quickly and responded to, without impacting the continuity of supply or impacting patient safety."

Security of the supply chain is critical for all companies that offer products and services to consumers, concurred Ettore Cucchetti, CEO of ACG Inspections, particularly in terms of counterfeit products, product damage or theft, and smuggling. "For the pharmaceutical industry, which is dealing with products and services directly impacting human health, supply chain security becomes more

Gribanov - stock.adobe.com

Supply chain risk and security maturity evolution

Discussing supply chain risk and security as a business led journey, Roddy Martin, chief digital strategist at TraceLink, explains the five stages of its evolution to *BioPharm International*:

- "**Stage 1.** Reacting to risk and security problems after the fact.
- **Stage 2.** Specialized security and risk management projects; for example, track and trace/serialization.
- **Stage 3.** Supply chain risk and security are a functional excellence capability; for example, risk and security requirements are codified into all work within functions like manufacturing, procurement, logistics, and so on.
- **Stage 4.** Supply chain and risk are codified as core "this is how we work" requirements in all horizontal, end-to-end, and cross-functional processes from the patient all the way back through the business into all elements of supply.
- **Stage 5.** Risk and security capabilities are embedded into and across the total ecosystem and network both internal and external to a company; the core capability is that product integrity, availability, and patient safety are regarded as a given. In stage 5, risk and security are both driven as value based capabilities rather than seen as a cost."

crucial in terms of a company's product integrity, brand image, and, ultimately, its bottom line," he says.

DIFFERENT APPROACHES

As Michael Pisa and Denise McCurdy reported in their policy paper in February 2019, at a basic level there are two traceability models that can be adopted (3). One model is to have a point-of-dispense verification approach where verification occurs at the top of the supply chain and then also at the bottom. The other model is full traceability, which is more complex in nature as the tracking and tracing of products occurs every time they change hands within the supply chain.

Many countries and regions have already signed a traceability approach into law, including China, India, Turkey, the European Union, and the United States, and approaches vary from country-to-country. "Verification and full traceability can both facilitate and improve supply chain security," says Widengren.

The EU and US, for example, chose the adopt different approaches. The former employing the point-of-dispense verification approach, while the latter is using the full traceability approach. "In the EU market, serialization requirements were implemented as part of the falsified medicines directive (FMD) regulation to protect the safety of patients," adds Widengren. "Essentially, through serialization, dispensers gain the ability to verify product legitimacy before a drug reaches the patient by scanning the unique identifier included on the pack.

"Whereas, track-and-trace systems can not only determine the authenticity of a product at the point of dispense, but also track the movement of products and prohibit falsified medicines from progressing through the supply chain," he continues. "Each partner involved in getting drugs to market can scan unique identifiers to access data around the journey of medicines and verify the authenticity of medicines as they move through the supply chain."

DEALING WITH DATA

Each traceability approach being implemented across the world has inevitably impacted industry, in particular as a result of the need to deal with vast amounts of data. "Due to the sheer amount of data generated by serialization requirements, organizations have been required to evaluate and adopt software technology solutions to create, capture, store, report, and share compliance data at scale," notes Martin. "This question of technology scalability remains a real concern when it comes to simply meeting the requirements of these legal mandates themselves, which is one of the critical reasons that a cloud-based, network platform is optimal," he continues.

In agreement, Widengren states that cloud-based networks have been found to be the most successful in terms of connecting supply chain partners and enabling the exchange of serialization data. "As well as enabling compliance with serialization regulations, these platforms also offer the opportunity for businesses to improve supply chain visibility and gain additional value from their investment," he says. "By giving companies greater insight into their operations, businesses can make more informed decisions in areas such as supply and demand forecasting, product recalls, and even achieve engagement with patients."

Additionally, Martin emphasizes that as industry looks to the future and leveraging the data gained from serialization, there will be a shift away from the fragmented silo nature of the bio/pharma supply chain that has existed previously as a fractious supply chain hinders visibility and impacts performance. "Instead, serialization should be used as a lens to look at the end-to-end digital supply chain and, if done right, will lead to transformative benefits in terms of increasing business value through more collaborative supply chains and end-to-end visibility into value networks," he explains.

"Blockchain will be considered as one of the critical factors when it comes to selecting a supply chain partner in the future," adds Cucchetti. "Product traceability and recalls are known to be the biggest challenges for most industries, and blockchain landscape can be used to secure the transaction between the supply chain partners. With blockchain, companies can address counterfeit issues through the authentication process, and they can perform product recall smoothly. This can help them to identify the issues in logistics and distribution channels, using the complete supply chain data to optimize the supply chain."

REGULATORY INITIATIVES

"Regulatory and government bodies are looking into all available and emerging technologies for securing supply chains," notes Cucchetti. "Each regulatory body has multiple objectives, but the preliminary goal remains the same—to secure the product from manufacturer to end consumer."

Giving some examples, Cucchetti highlights Russia, which has mandated crypto tail into barcoding processes; Indonesia, which is assessing product authentication techniques; and the US, which is looking to evaluate blockchain with serialization. "Currently, most of the regulatory requirements are focused towards serialization and track and trace, as well as mandates for the pharmaceutical industry," he says. "Going forward, it is likely that similar regulations will be applicable to all other industries as well. Government and regulatory bodies will be more stringent in regulation—considering consumer health and safety requirements. As the technologies evolve, each government will be evaluating possible technological implementations to secure supply chains to fight against counterfeiters, and also to have complete visibility of the industry."

Specifically focusing on the US and its exploration of methods to enhance the safety and security of the supply chain, Martin discusses FDA's Drug Supply Chain Security Act (DSCSA) pilot program. "Recently, FDA announced a pilot program project seeking innovative and emerging approaches for enhanced tracing and verification of prescription drugs in the US to ensure suspect and illegitimate products do not enter the supply chain," he confirms. "TraceLink was accepted into the pilot program and will focus on two workstreams; blockchain and digital recalls."

Companies of varying sizes will be included in the TraceLink pilot project, covering the end-to-end supply chain. "Together, through network connectivity and innovative software solutions, participants will explore and collaborate on ways to improve the safety and security of the drug supply chain and will use early stage technology to do so," Martin adds.

SAFEGUARDING FUTURE SUPPLY CHAINS

"Companies should always be mindful of new ways they can safeguard their supply chains, especially when the political landscape is in a state of flux," emphasizes Widengren. "It is essential to consider long-term prospects so that a plan can be made around new legalities. As such, pharmaceutical manufacturers should invest time into understanding the markets they operate in, as well as the ones they may potentially pursue. This way they can design a strategy that will help facilitate market entry and progression with as little complexity and limitation possible."

For Cucchetti, a proactive approach to supply chain security is key as it can afford companies time to be able to adapt to all changes required when complying with regulations. "Companies should form a dedicated team with all business functions involved in the serialization project, documenting all regulatory and business requirements," he says. "At all times, organizations should work alongside the implementation partner and possibly with the regulation bodies to understand the upcoming changes and work towards accommodating them."

As a final note, Widengren explains that for companies to be able to reap the benefits of supply chain security requirements and for optimum preparedness and future safeguarding, companies should consider implementing aggregation capabilities. "Aggregation is not always a mandatory measure," he summarizes, "but it is expected to become part of legislative requirements in the future."

REFERENCES

1. WHO, "A Study on the Public Health and Socioeconomic Impact of Substandard and Falsified Medical Products," Report, November 2017.
2. Strategy&, "Fighting Counterfeit Pharmaceuticals New Defenses for an Underestimated—and Growing—Menace," Report, June 29, 2017.
3. M. Pisa and D. McCurdy, "Improving Global Health Supply Chains Through Traceability," Center for Global Development Policy Paper 139, February 2019. ◆

INVESTMENT IN INTEGRATED BIOLOGICS DEVELOPMENT

Catalent Biologics provides advanced technologies and tailored solutions for biologic development from DNA to commercial supply. Catalent recently commenced a $200-million investment to expand drug substance and drug product manufacturing capacity at its Madison, WI and Bloomington, IN sites. The expansions were in response to increasing demand from existing and future customers following the company's 30th commercial product approval. **Catalent,** 14 Schoolhouse Road, Somerset, NJ 08873 USA, tel: +1.888.765.8846, solutions@catalent.com, www.catalent.com

DISTEK, INC.

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

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

NGC PLATFORM

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

DELIVERING CONFIDENCE IN QUANTITATIVE MICROBIOLOGY

BIOBALL is a small water-soluble ball containing a precise number of microorganisms delivering unprecedented accuracy for quantitative microbiological quality control. BIOBALL is easy to use and requires no preparation or pre-incubation and is an accredited reference material under ISO Guide 34 standards. www.bioball.com, **bioMérieux, Inc.,** www.biomerieux-usa.com

Ask the Expert — *Contin. from page 46*

The most important and critical element for OOS investigations is specifying the timeliness. This should be stipulated in the SOP and, in most cases, the investigation into the OOS, from the laboratory perspective, should be concluded in 24 hours or less. The expectation of when the contract lab will inform you of any OOS obtained should be clearly defined in your quality agreement. The sooner a laboratory error can be ruled out as the cause of the OOS result, the sooner the investigation can be started.

Taking the time to establish a quality agreement and investigate the details of their OOS procedure is the first step in establishing a good working relationship with your contract test laboratory. The final product testing procedure for OOSs isn't the only one you need to review, however. You should also look at the quality agreement and OOS procedure being used by your manufacturer for in-process test results, assuming they are different entities. The same information required in the final product OOS procedure should be the same for in-process testing.

REFERENCES

1. 21 *CFR* 200.10 (b)
2. FDA, *Contract Manufacturing Arrangements for Drugs: Quality Arrangements: Guidance for Industry* (FDA, November 2016).
3. European Commission, *The Rules Governing Medicinal Products in the European Union, Volume 4*, EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use, Chapter 7, Outsourced Activities (EC, January 31, 2013).
4. EC, *EudraLex, The Rules Governing Medicinal Products in the European Union, Volume 4*, EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use, Part 1, Chapter 6: Quality Control (EC, October 2014).
5. EC, *EudraLex*, Volume 4, Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Part II: Basic Requirements for Active Substances used as Starting Materials (EC, September 2014).
6. FDA, *Guidance for Industry, Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production* (FDA, October 2006). ◆

Ad Index

Ask the Expert

Quality Agreements and Out-of-Specification Investigations

A good working relationship between sponsor and contractor will become invaluable when an OOS occurs.

Susan Schniepp is executive vice-president, Post-approval Pharmaceuticals and distinguished fellow at Regulatory Compliance Associates.

Q. I'm responsible for quality at a small, virtual startup company and am working on documentation to contract out our product testing. What information is there regarding quality agreements and laboratory investigations?

A. The best place to start is to take a critical look at existing guidance documents and regulations that govern quality agreements and out-of-specification (OOS) investigations. The basic philosophy when establishing any quality agreement is to understand that the contract provider and contract giver are partners and their behaviors reflect on each other.

The 21 *Code of Federal Regulations* (*CFR*) 200.10(b) confirms this concept by stating: "The Food and Drug Administration is aware that many manufacturers of pharmaceutical products utilize extramural independent contract facilities, such as testing laboratories, contract packers or labelers, and custom grinders, and regards extramural facilities as an extension of the manufacturer's own facility" (1). FDA's *Contract Manufacturing Arrangements for Drugs: Quality Agreements*. Section B, Elements of a Quality Agreement, Part e. Laboratory controls, states that a quality agreement should include: "Designation of responsibility for investigating deviations, discrepancies, failures, out-of-specification results, and out-of-trend results in the laboratory, and for sharing reports of such investigations" (2). This confirms that the responsibility for OOS investigations is shared and communication between the contract giver and contract provider is critical. The European Union also addresses the need for a relationship between you and your outsourced laboratory in *EudraLex*: "The Contract should describe clearly who undertakes each step of the outsourced activity, e.g. knowledge management, technology transfer, supply chain, subcontracting, quality and purchasing of materials, testing and releasing materials, undertaking production and quality controls (including in-process controls, sampling and analysis)" (3).

These regulations establish the need for quality agreements that cover laboratory activities but don't define what needs to be in an OOS procedure. The EU addresses the need to investigate OOSs in their GMPs. *EudraLex* Part 1, Section 6.35 states, "Out of specification or significant atypical trends should be investigated. Any confirmed out-of-specification result, or significant negative trend, affecting product batches released on the market should be reported to the relevant competent authorities. The possible impact on batches on the market should be considered in accordance with Chapter 8 of the GMP Guide and in consultation with the relevant competent authorities" (4). Part 2 of the EU GMP guide for APIs states in section 11.15 that: "Any out-of-specification result obtained should be investigated and documented according to a procedure. This procedure should require analysis of the data, assessment of whether a significant problem exists, allocation of the tasks for corrective actions, and conclusions. Any re-sampling and/or retesting after OOS results should be performed according to a documented procedure" (5).

FDA's *Guidance for Industry, Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production* (6) clearly defines the responsibilities for the laboratory analyst and supervisor, which should be reflected in any laboratory OOS procedure. A well-written standard operating procedure (SOP) on OOSs should require investigations to be thorough, timely, unbiased, well documented, and scientifically sound. Often, the procedure will contain a checklist that assists in identifying obvious laboratory errors. The checklist assesses the suitability of analyst qualification and training, use of correct procedure and specification, the calibration and performance of the equipment, correct preparation of test solutions and dilutions, use of proper reagents and standards, calculations, etc. A thorough checklist and analyst documentation are critical in identifying true laboratory error. The SOP should also discuss the sample retesting requirements when a true laboratory error is determined to be the cause of the OOS.

Contin. on page 45

Fanatic Studio/Getty Images

Informatics for Your Lab – LIMS • ELN • LES

Built Better for Pharma

LabVantage Pharma is the only pre-validated, pre-configured, 100% web-based informatics platform designed specifically for pharmaceutical QA/QC manufacturing. It is also the first LIMS to enable compliance with global draft guidance for data integrity.

With an embedded LES; purpose-built functionality such as stability testing, lot genealogy, quality dispositioning, and environmental monitoring; and configurable without coding, LabVantage Pharma gets pharma labs up and running faster, at reduced cost and risk.

If a pharmaceutical lab needs it, LabVantage Pharma is built better to handle it.

LabVantage®

GET THE LABVANTAGE ADVANTAGE:
LabVantage.com/pharma

CREATING BIOLOGIC TREATMENTS IS SCIENCE. ORCHESTRATING FASTER DEVELOPMENT IS ART.

Introducing our latest masterpiece, OneBio℠ Suite, which integrates development through complete clinical and commercial supply to simplify, accelerate and de-risk your biologic development.

With our deepest expertise and advanced technologies, we help you deliver better biologic therapies to patients, faster. **Catalent, where science meets art.**

Catalent®
BIOLOGICS

us + 1 888 SOLUTION (765-8846) **EU** 00800 8855 6178 catalent.com/onebio