SCIENCE FOCUS FUELS SUCCESSFUL PROCESS DEVELOPMENT FOR STARTUPS

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DEMONSTRATING RESULTS WITH ANTIBODY-DRUG CONJUGATES

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ANALYTICS
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COVER STORY

10 Science Focus Fuels Successful Process Development for Startups

Getting the science right helps biopharma startups overcome development and commercialization challenges.

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Promoting patient compliance with drug regimens extends beyond the formulation laboratory.

Keeping the Patient and Public Health in Focus

The seasonal flu was widespread in my geographic area during the 2018–2019 winter, and despite receiving a flu shot five months ago, I developed symptoms. The Centers for Disease Control (CDC) estimates that 31–36 million people experienced seasonal flu illnesses in the 2018–2019 flu season, prompting an estimated 16.8 million doctor visits, a half million hospitalizations, and up to 46,800 deaths. Based on CDC estimates, the 2018–2019 season was the second most severe in the number of illnesses and doctor visits, fifth in hospitalizations, and fourth in deaths, when compared with other flu seasons dating back to 2010 (1).

An estimated 169.1 million doses of flu vaccine were distributed in the 2018–2019 season, an increase of almost 9% over the previous season (2). I was fortunate; my symptoms were mild, and I stayed home from work for a week to prevent the spread of the illness. Still, I was an unhappy patient. Sorting through the many options of over-the-counter (OTC) medicines was dizzying. Dosing instructions were confusing. And the prescription and OTC medicines I took literally left a bad taste in my mouth.

While my illness was routine and I soon recovered, the implications for patients with serious medical conditions who do not adhere to complex dosing regimens can be health- or life-threatening. Therapies that require painful injections, administration by trained medical professionals, or have adverse side effects are just a few challenges to effective dosing of drugs.

Patient-centric drug design—bringing the patient’s experience to the forefront of drug formulation strategies—is an emerging focus for drug companies. Development strategies should include more than just studying the biopharmaceutical and physicochemical characteristics of a drug molecule, experts say. Understanding the patient’s physical and dosing needs at early stages of development will be crucial. I will be moderating a panel discussion on patient-centric drug design at CPhI North America in Chicago on April 30, 2019. Visit www.cphi-northamerica.com for more information.

Measures beyond medicine

Practical measures such as isolation of an infected person and vaccinations can help contain disease outbreaks. However, many people choose to not get vaccinated against common diseases due to both medical and non-medical concerns. Measles, a disease that was declared eliminated from the United States in 2000, is making a comeback, with a spike in reported cases in 2019.

Through mid-March 2019, the CDC reported more than 300 confirmed cases of the disease in 15 states, up from 17 cases in 2018. The outbreak was attributed to international travelers bringing the disease to the United States as well as clusters of unvaccinated people in certain communities.

An outbreak in Rockland County, New York prompted county officials to declare a state of emergency that barred anyone under age 18 who was not vaccinated against the measles from public places for 30 days or until they receive a vaccination (3). Officials told media outlets the measures were taken to get the public’s attention and encourage more vaccinations. Backlash against the emergency order, however, illustrated that opinions about a patient’s right to refuse treatment are strong and present challenges for public health officials, adding another layer of complexity to promoting patient adherence to drug regimens.

References
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Regulatory authorities in the United States and other regions are encouraging investment in continuous manufacturing (CM) processes to better ensure quality drug production, avoid shortages, and ultimately lower the cost of medications for patients. The aim is to support an industry shift away from step-wise batch production, which is vulnerable to contamination, errors, and stoppages, to the use of automated modular systems better able to reduce human error, waste, and delays.

As of January 2019, FDA has approved five products from four manufacturers that use CM systems. These involve small molecules, but more comprehensive CM processes are in development for proteins and biologics. FDA reports that approximately 20 companies—both brand and generic—are talking to agency staff about developing and implementing CM processes.

To spur more manufacturers to join the trend, FDA published new draft guidance in February 2019 that clarifies its policy regarding CM approaches (1). The aim is to address manufacturer concerns that adoption of CM technology could delay approval of new drug applications or complicate switching from a batch to a CM process for marketed products, explained then FDA Commissioner Scott Gottlieb and Janet Woodcock, director of the Center for Drug Evaluation and Research (CDER), in a statement highlighting agency efforts to expand industry investment in modern manufacturing systems (2).

The new guidance provides advice on what process and control strategy designs, including equipment, are needed to meet regulatory considerations. The guidance applies to CM for drug substances of all finished dosage forms, including drugs, generic drugs, and over-the-counter products, but not to biologics. It aims to clarify definitions of batches, process validation, and quality systems considerations for CM and to provide recommendations for scaling up production and demonstrating stability for finished drugs produced with CM systems.

To overcome company concerns about the cost of investing in new production technologies, FDA emphasizes that CM platform technology can be used to manufacture multiple products, which can help reduce the risk of drug shortages and facilitate scale-up of production when needed. An added benefit is the smaller footprint for CM systems, along with greater efficiency and consistency in these operations.

Gottlieb and Woodcock also cite increased FDA funding for private organizations assessing CM technology in laboratories, as well as support for internal agency investigation of CM and other technologies. CDER’s Emerging Technology Team (ETT) also is providing additional help for early adopters of CM in implementing new technology and navigating the application review process for products made with these modern methods. Additional funds in FDA’s 2019 budget will support further development of a standard operating approach for CM and advanced manufacturing, with the overall aim of reducing dependence on the import of pharmaceutical ingredients and products to better assure quality and supply.

At the same time, the International Council for Harmonization (ICH) is moving forward to establish standards for continuous manufacturing of drug substances and drug products, with the aim of developing a common framework for regulating and approving products that utilize CM methods. ICH approved a concept paper on the topic at its November 2018 meeting, and a panel of experts is mapping plans for developing a new quality
guideline (Q13) on this topic. The aim is to establish common definitions for CM, articulate key scientific issues, and harmonize regulatory concepts and expectations across the regions. Participants hope to complete the project by the end of 2021, after conducting a series of site visits to CM facilities for both small and large molecules and learning more about state-of-the-art technologies. The expert working group includes representatives of industry and regulatory authorities in the United States, Europe, Japan, Canada, China, Korea, Singapore, and other nations.

BRINGING IN BIOLOGICS

While most CM operations so far have involved small molecules, manufacturers of biologics also are assessing how CM may apply to both upstream and downstream biotech production. This topic was examined in depth at the January 2019 CMC Strategy Forum on Continuous Manufacturing for Biologics organized by CASSS (3). Industry experts discussed advances in implementing CM for small molecules, noting that adoption of this approach in biomanufacturing has been limited largely to upstream “hybrid” approaches. BioMarin Pharmaceutical vice-president, Novato Operations, Erik Fouts noted that equipment manufacturers are offering small and pilot-scale CM systems for integrated continuous upstream and downstream processes and that these approaches are drawing interest as ways to boost productivity, lower the manufacturing footprint, and avoid waste in raw materials.

Participants at the Forum supported the ICH effort to develop the Q-13 guideline on CM as important in encouraging flexible approaches for implementing CM in manufacture of small molecules and therapeutic proteins. The aim is to clarify regulatory concepts, such as batch, process validation, and continuous process verification. While CM has the potential to increase flexibility and robustness in biomanufacturing, and to reduce costs and product heterogeneity, challenges remain in assuring sterility and advancing process controls.

These issues were addressed more broadly at the CASSS WCBP 2019 Scientific Program (4). The three-day program concluded with a review of initiatives to achieve flexible and modular facilities and the use of process analytical technology (PAT) in continuous manufacturing. PAT for an integrated continuous biomanufacturing platform is “becoming a reality today,” the experts concluded, noting that there remain many questions to consider in the journey to flexible and modular facilities.

REFERENCES


FDA Takes Steps to Refine Biosimilar Naming Convention

On March 7, 2019, then FDA Commissioner Scott Gottlieb, MD, announced an update to FDA’s policy for determining the naming convention for biosimilars in an effort to balance competition on the market and help ensure patient safety.

The agency is releasing a draft guidance to explain that:

• It no longer intends to modify the proper names of biological products that have already been licensed or approved under the Public Health Service Act without an FDA-designated suffix in their proper names.

• The agency does not intend to apply the naming convention to the proper names of transition biological products.

• Going forward, for interchangeable biosimilars, FDA intends to designate a proper name that is a combination of the core name and a distinguishing suffix that is devoid of meaning and composed of four lowercase letters.

Gottlieb stated in a press release that this framework will help secure pharmacovigilance so that the agency can effectively monitor all biological products in the post market—originators and biosimilars—and promote patient safety. To facilitate adverse event-report tracking, originator, biosimilar, and interchangeable products will have nonproprietary names that are distinct from each other.

—The editors of BioPharm International.
Process development can be challenging at the best of times, even for the most established companies with deep resources. Emerging biopharma companies working to develop novel gene and cell therapies face even greater obstacles. They lack access to revenue streams from existing drug sales to fund their process development efforts, so money must be raised, which requires convincing investors that the ideas they are developing will become successful products and provide a healthy return.

Young companies also often have more difficulty attracting the necessary skilled talent. And company owners and managers are often so involved in getting established that process development becomes an afterthought, rather than being implemented as early as possible to determine what it will require to make the translation from concept to commercial product really happen. Unknown companies also don’t attract the attention of equipment and material vendors, and it can be difficult to demonstrate credibility and convince suppliers to invest in new relationships.

WHAT IS PROCESS DEVELOPMENT FOR EMERGING BIOPHARMA?
For emerging biopharma companies developing next-generation therapies, process development can have several different meanings. BriaCell Therapeutics (BriaCell) is an immunoncology company that develops novel targeted immunotherapies for multiple cancer indications. These immunotherapies include Bria-IMT and Bria-OTS, which consist of cancer cell lines with the capability to directly present cancer antigens to the immune system and further stimulate the immune system with stimulatory factors. For BriaCell’s CEO, Bill Williams, there are three aspects to process development: process development in the production of its novel therapeutics (both drug substance and drug products), in the design and implementation of clinical trials, and in the selection of new drug targets.

In the context of cell therapies, process development is a uniquely important space because it is such a new and evolving
field, according to Armon Sharei, CEO of SQZ Biotech, a company developing cell therapies for immuno-oncology and autoimmune indications using its proprietary SQZ cell therapy platform, also known as cell squeezing. “There are no established protocols for how to go about process development for cell therapies, unlike for conventional biologics and small-molecule drugs. We are engineering patient cells to produce a response inside that specific patient. Given the cost and time involved, being able to develop a practical and scalable process is essential to achieving success,” Sharei explains.

For Krystal Biotech, which is developing gene therapies for skin diseases using a new vector for delivery, process development has involved cell-line engineering as well as determination of the optimum process for production of the viral vector, according to founder and chief operations officer Suma Krishnan. “We built a GMP facility to manufacture the products entirely in-house, so process development was a fundamental activity for us,” she adds.

IN-HOUSE OR OUTSOURCE?
The decision to build its own facility was based on the determination that an external vendor could not be relied on to develop a process for the new type of vector Krystal Biotech is focusing on, according to Krishnan. The company first built an inhouse process development group to establish the optimum process, then transferred that final process to a contract manufacturing organization.

SQZ Biotech, after debating early on, chose also to conduct all of its process development work in-house. “Our decision went back to the fact that cell therapies are an emerging area and the process has a direct impact on the viability of the commercial model. We did recognize that we needed to build process development expertise, so our efforts began three years ago. The work has paid off; we will be going into the clinic in 2019,” observes Sharei.

Celyad, a company developing chimeric antigen receptor (CAR)-T cell therapies, built on its previous work with a stem-cell therapy that it took from preclinical development to two Phase II trials in Europe and FDA approval for an investigational new drug (IND). “What we learned while carrying out tech transfer, scaling up the process, and manufacturing over 300 autologous clinical batches that were then delivered to close to 10 countries served as a basis for our decision to keep internal all process development activities for CAR-T cell products,” notes Jean-Pierre Latere, chief operating officer of Celyad.

BriaCell, meanwhile, has generally overseen process development for production of its therapeutics, working with clinical research organizations (CROs) that have tremendous experience in the development of cellular therapies and in collaboration with regulatory experts, according to Williams. For the implementation of clinical trials, BriaCell designs the studies and selects the CROs to implement them. The clinical investigators are generally responsible for patient recruitment and treatment. “It all falls into place based on who possesses the appropriate expertise and access to the corresponding resources,” says Williams. New drug target selection and the design of strategies to develop effective drugs against these targets are done entirely in-house at BriaCell.

CHALLENGES: FROM FUNDING TO VENDOR RELATIONSHIPS
The technical aspects involved in the development of processes for the production of next-generation therapies can be challenging on their own. Emerging biopharma companies face many others as well.

The biggest challenge for BriaCell has been accessing funding, according to Williams. “We possess the intellectual resources for both selection of new drug targets and clinical trial design, and have access to the proper expertise and facilities for therapeutic development and drug production. “The main problem is convincing investors that we have ideas that will result in viable therapeutics. The process of drug development is a long one due to tight regulations by the regulatory bodies in the United States and Europe, and hence, biotechnology is not a suitable investment for an investor who expects a quick return on investment in a short period of time,” he explains. But he notes that patience can be amply rewarded, as it was for him when he was at Incyte Corporation, where the stock price rose from $2–3 per share in 2009 to more than $110 per share in 2015.

Accessing talent, which is crucial in process development for cell-based therapies, can also be a challenge, according to Latere. “Because cell therapy is a new field, there are few people with a lot of experience and expertise. Complicating this situation is the fact that the mindset for process development of cell therapies can be quite different from that needed for process development of traditional biologics and small-molecule drugs,” adds Sharei. Reliance only on private funding can make it difficult to attract people as well, according to Krishnan.

Finding appropriate commercial equipment is a third challenge. Because few cell and gene therapies have yet to be approved, most work has been performed in laboratory equipment; commercial solutions are limited to a few plug-and-play options, according to Sharei. Establishing relationships with and between vendors can help tackle challenges in process transfer, a lesson that Krishnan learned through difficult experiences. “It is challenging for new biopharma companies to establish the partnerships with multiple vendors that can significantly facilitate process development and process transfer,” she says.

On the technical front, predicting process capability and performance is another important challenge, while scaling up lab processes also carries an element of risk, according to Latere. He gives as an example large-scale cryopreservation, which can result in a significant level of stress on cells leading to challenges during the final step of clinical
manufacturing. In addition, development work at Celyad is usually performed with healthy donor materials such as blood and bone marrow taken via apheresis; clinical manufacturing deals with starting materials collected from patients with various diseases, sometimes with complex medical histories or medication profiles that can impact cell biology and affect certain cell functionalities, all of which can lead to unpredictable clinical manufacturing, according to Latere.

Celyad has also observed cell fratricide (cells killing each other or even committing suicide) during the culture of CAR-T cells, which lowers the manufacturing success rate and requires important process changes to tackle cell fratricide during a clinical trial. Optimizing cell yield is crucial in cell therapies because cell yield has a direct impact on the quantity of cells available for administration to the patient. “Unlike with batch processes where maximizing the yield affects cost, maximizing the yield of cell therapies directly impacts the performance for the patient. It is important to select the best equipment and develop a process that minimizes losses, from choosing the shortest plastic tubing to minimizing the number of process steps,” Sharei explains.

Another issue for autologous cell therapies is the need to scale out, rather than scale up. When moving from preclinical to early clinical studies, the process must be scaled to work for one patient. Manufacturing the cell therapy for many different patients requires the process to be repeated in parallel—or scaled out. There is no opportunity at that time for further process optimization, so it is important to be thoughtful about process development early on, according to Sharei.

Lastly, the quantity of effort required can be daunting, according to Krishnan. “We have a team comprised of only a few people, so it took many long hours, endless experiments, and learning from our mistakes,” she says. On the other hand, she notes that the small group was nimble, very focused, had great tenacity, learned quickly, and was able to make great strides in improving the yield, purity, efficacy, and cycle time, and ultimately developed a process suitable for the manufacture of clinical material.

CONVERTING CHALLENGES TO OPPORTUNITIES

While emerging biotechs face these numerous challenges, they also have some advantages over established pharma companies and can in some cases convert those challenges into opportunities.

Emerging biotechs are more likely to hit on novel ideas that are actual game changers in the industry, according to Williams, because fewer people are involved in making decisions compared to those at larger companies. “Ideas are more easily discussed with the decision makers, and changes in the strategy, acquisition, and development of novel therapies can be implemented more rapidly at smaller firms. Additionally, emerging biotechs tend to operate more cost-efficiently compared to their larger counterparts,” he says.

Adversity can also lead to creativity and success, according to Krishnan. “Because we had to use a brute force approach, conducting many countless experiments, we learned a tremendous amount about the process. In addition, it was often necessary to think ‘outside the box’. With the extensive knowledge and expertise we have gained about our unique viral vector, we now have a smoother path forward. In addition, we have established an extensive set of trade secrets available for future development efforts,” she observes.

MANY LESSONS LEARNED

Learning from mistakes is perhaps one of the most important lessons that any emerging biopharma company should take to heart. “It is important to continually evaluate processes and continually improve them. Mistakes happen and are actually needed to fuel future directions almost as much as new insights gained,” Williams says. He also advises emerging biotech companies to cultivate good relationships with their investors and make sure they understand the company’s vision and its potential.

BriaCell has also learned to select novel therapeutics with new strategies based on the best science available and to cultivate an in-depth understanding of the field of cellular immunotherapy that builds on the experience of multiple investigators in the field. “This strategy has permitted us to streamline our approach to clinical trials, targeting the patient’s most likely to benefit from our therapies,” comments Williams. “Overall, we have learned that expertise is the main key to success and how to locate and exploit it,” he adds.

For Latere, too, understanding the science supporting a product is paramount. “As a start-up develops, ensuring the supporting cast puts an emphasis on the underlying science and the ability to translate such science into a desirable product that can be manufactured consistently is key,” he notes. He goes on to add that it is important to dare to challenge conventional wisdom and not be stopped by engineering challenges, as they are solvable, while scientific flaws are not.

On a similar note, Sharei observes that it is important to be comfortable implementing custom manufacturing systems. “As long as you know the problem you are trying to solve and are designing for GMP manufacturing, developing proprietary systems can provide significant advantages, particularly in nascent fields such as cell and gene therapy,” he remarks. “The systems we have implemented have tremendous advantages over commercially available equipment on the market. Investing in the system at the right time and with confidence can have a huge impact,” Sharei adds. Similarly, he points out that establishing a manufacturing site early and initiating technology transfer and training as early as possible will ensure that a company is well-prepared to move into the clinic when the time comes.

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Demonstrating Results with Antibody-Drug Conjugates

Drug makers continue to explore innovative ways to develop antibody-drug conjugates based on their unique potential to neutralize cancer cells.

FELIZA MIRASOL

Though antibody-drug conjugates (ADCs) have had a difficult time getting off the ground, their mechanism of action shows great potential for neutralizing cancer cells. Drug developers are focusing on manufacturing improvements to address some potential safety concerns posed by ADCs, as they work to demonstrate clinically significant therapeutic benefits.

Currently, only four ADCs have been approved by the FDA for sale in the United States:

- Adcetric (brentuximab vedotin), developed by Seattle Genetics, which was approved in August 2011
- Genentech’s Kadcyla (ado-trastuzumab emtansine), which was approved in February 2013
- Besponsa (inotuzumab ozogamicin), which was developed by Pfizer and approved in August 2017
- Mylotarg (gemtuzumab ozogamicin), also developed by Pfizer, which FDA approved a second time in September 2017 after Pfizer voluntarily withdrew the drug from the market after its initial FDA approval in May 2000. The withdrawal was due to the company’s inability to verify a clinical benefit with the product soon after the initial approval in 2000. There were also safety concerns under consideration (1) and because of safety concerns.

TARGETING CANCER

ADCs are made up of an antibody that is linked to a cytotoxic agent by a biodegradable compound. While they are designed to eliminate fast-growing cancer cells, ADCs can also harm healthy proliferating cells, resulting in adverse patient reactions and side effects. Manufacturers are discovering different ways to reduce these side effects by finding different ways to configure the antibody and the chemotherapy portions of the compound. In some cases, for example, the entire ADC may be linked with a second cytotoxic agent, an approach that is allowing some ADCs...
to target cancer cells directly while avoiding harm to surrounding healthy cells (2).

The antibody component of the ADC is specific to tumor cell-surface proteins, which give ADCs tumor specificity and a potency that was previously believed to be impossible to achieve with traditional drugs. Ongoing ADC development efforts are now focusing on identifying better targets, determining more effective cytotoxic payloads, and further improving the way that the antibody and cytotoxic drug are linked. Improving the understanding of the mechanistic basis by which ADCs act should allow drug manufacturers to design rational combinations of ADCs with other agents, including immunotherapy treatments (3).

**CHALLENGES TO DEVELOPMENT**

Developing ADCs has been particularly challenging. In order for the compound to outperform an ordinary chemotherapy drug, the ADC must:

- Be able to target cell-surface proteins with tumor-specific membrane expression
- Be stabilized by a linker that keeps the cytotoxic payload attached during circulation but permits release of the load after cellular internalization
- Contain a cytotoxic that effectively kills tumor cells (3).

Early development of ADCs was hampered by several pharmacological and safety issues. A key factor was conjugation stability, according to David Simpson, CEO of Iksuda Therapeutics, a UK-based company that specializes in creating next-generation ADCs. The molecule’s inherent instability can lead to premature release of the cytotoxic payload, with profoundly negative effects on the therapeutic index (TI). The ultimate result is reduced efficacy and tolerability, Simpson explains.

Iksuda addresses molecular instability in ADCs in a number of different ways, including through its use of PermaLink conjugation technology, which results in a simple yet fundamental change in chemistry. The result: highly stable ADC constructs, developed via a concept the company terms “stability by design.”

**Ongoing ADC development efforts are now focusing on identifying better targets, determining more effective cytotoxic payloads, and further improving the way that the antibody and cytotoxic drug are linked.**

“Tumor-directed toxicity of its payload and tolerability profiles,” Simpson states.

The overall “power” of ADCs also remains a major hurdle to development. This “power” is driven by the payload’s ability to elicit its potent cell-killing activity in a broad range of tumor types—ultimately targeting the broadest possible patient population,” Simpson says. He notes that the industry currently has limited availability of payloads that are proving safe and effective in the clinic. Nevertheless, manufacturers continue to strive for ultra-potent toxin classes with novel modes of action to combat the emergence of drug resistance and the ongoing challenge of treating unyielding solid tumors.

“By focusing its attention on this challenge, Iksuda has leveraged the stability of the PermaLink conjugation platform to gain access to potent DNA alkylating payloads, incorporated into its lead ADC, as well as developing its own proprietary ultra-potent payload platform with a previously untapped mode of action for future ADC programs,” says Simpson.

**CANCER-KILLING MECHANISM**

As an emerging class of targeted therapeutics, ADCs have the potential to improve TI over traditional chemotherapy. “By combining the targeting power of antibodies with the cell-killing capability of potent cytotoxic molecules, it is possible to kill cancer cells more effectively while reducing debilitating side effects,” notes Simpson.

In broad terms, the anti-cancer activity of an ADC is driven by the toxicity of its payload and tolerability in patients depends on the stability of the conjugation chemistry and tissue distribution of the antigen (i.e., whether the target is present in healthy tissue or not). “This tumor-directed delivery system is designed to reduce off-target toxicity by limiting exposure of normal tissues to the cytotoxic payload. Stable conjugation chemistries (e.g., PermaLink), novel mechanisms of action, and highly potent toxins are being developed to increase the TI of ADCs,” he states.

Meanwhile, the limitation of antibodies has been their ability to complement their highly specific targeting capabilities with an equally matched ability to induce apoptosis. “An ADC’s ability to effectively exploit the targeting capabilities of the antibody whilst...
‘supercharging’ its cell-killing capabilities by the addition of a cytotoxic payload has broadened the application for the use of antibodies and revolutionized the use of alternative targeting moieties and scaffolds. The combined success of these therapeutic classes will dramatically improve the therapy options for cancer and particularly those of an aggressive nature,” according to Simpson.

The ADC field has been quick to respond to the rapidly shifting oncology drug preferences, which are now focusing on combination therapies. Checkpoint inhibitors had raised hopes for improved clinical outcomes. Despite their early promise, these drugs have shown variable effectiveness in treating solid tumors, and are more effective when used in combination with another therapeutic. ADCs might show considerably greater efficacy when used in combination with existing treatment regimens to give greater efficacy, and this approach would not worsen any debilitating side effects, Simpson points out.

By using the antibody’s ability to specifically target tumor tissue rather than healthy, normal tissue, ADCs can deliver highly potent cytotoxic payloads directly to the tumor site. “ADCs allow clinicians to target solid tumors specifically, with previously unobtainable dose levels of the active, cell-killing reagent, without exposing healthy tissue to its affects. Iksuda’s approach to conjugation chemistry allows manufacturers to enable the safe use of ultra-potent cytotoxic payloads. It thus raises the bar on the TI of ADCs and their clinical benefits to patients,” remarks Simpson.

REGULATORY CONSIDERATION
Composed of both biologic and small-molecule components, ADCs are complex entities. Their regulatory review also follows a complex path that has been specifically designed to ensure patient safety, Simpson explains.

“ADCs require review by both the Office of New Drug Quality Assessment (ONDQA) and the Office of Biological Products (OBP). Both offices have responsibility for Drug Substance and Drug Product and as with any emerging product class, ADC developers have worked closely with FDA to develop and drive the regulatory pathway,” he says, pointing out that the yearly increase in investigational new drug submissions for ADCs is a testament to the dedication of both drug developers and regulatory bodies to prove the value of these therapeutics in the clinic.

“ADCs allow clinicians to target solid tumors specifically.”
—David Simpson, Iksuda Therapeutics

“To date, and with the notable exception of the currently approved products, the therapeutic window for ADCs remains disappointing. In the recent past, clinical trials have been discontinued due to dose-limiting toxicities. This was seen with rovalpituzumab tesirine [Rova-T] and vadamustib talirine, for example, each of which has a pyrrolobenzodiazepine dimer payload),” he says. However, he believes that ADCs present a valuable and viable opportunity in the armoury against cancer, drug developers continue to reflect and learn from success and, importantly, failure in order to develop ADCs with sufficiently wide TI.

NEXT-GEN HOPES
Drugmakers that are working on optimizing ADCs are learning from past failures as they continue to push for innovation, in the form of next-generation ADC drug development. As a result, the next generation of ADC is broadly considered to have a significantly wider therapeutic window, Simpson remarks.

These next-generation ADCs are more stable, contain highly potent payloads with broad activity, and are more homogeneous than the previous generation. Therefore, they are less influenced by differential clearance rates when compared to those ADCs that are currently well advanced in clinical development programs. “While the field recognizes that there is no ‘one box for all’ approach for ADCs, significant focus has been given to site-specific conjugation which allows for a homogeneous ADC that is generally more systemically stable with a concomitant improvement in PK [pharmacokinetics],” Simpson says.

Even though only four ADCs are on the market, Simpson notes that more than 40 site-specific drug conjugate technologies have been developed. While the ADC field has historically been dominated by the use of auristatins (e.g., monomethyl auristatin, or MMAE) and maytansines (e.g., DM4), next-generation ADCs are moving toward more potent payloads with DNA damaging mechanisms of action. Examples include duocarmycins, pyrrolobenzodiazepine dimers, and indolinobenzodiazepine dimers).

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Biotherapeutics are frequently glycosylated, and the structure of N-glycans attached to the protein can potentially affect immunogenicity, pharmacokinetics, and pharmacodynamics. This can make glycosylation a potential critical quality attribute (CQA); the characterization of N-glycans is an essential part of the development process.

This webcast will present rapid N-glycan sample preparation workflows for biotherapeutics, including labeling of released N-glycans with InstantPC, a glycan dye that provides high signal for fluorescence (FLR) and mass spectrometry (MS) detection, and 2-AB, a traditionally-used N-glycan fluorophore. Analysis of labeled N-glycans is shown using separation by hydrophilic interaction liquid chromatography (UHPLC-HILIC) coupled with FLR and MS detection, and a capillary electrophoresis (CE)-based platform for N-glycan screening. Topics to be addressed include:

- Rapid sample preparation approaches for N-glycans (1–2 hours)
- LC/FLR and LC/MS analysis of released N-glycans
- Screening of N-glycans using a CE platform with a 2-minute run time

**KEY LEARNING OBJECTIVES**

- Importance of N-glycan analysis for biotherapeutic proteins
- Choosing a fluorescent dye and analytical separation method for N-glycans
- Use of glycan standards

**WHO SHOULD ATTEND**

- Biopharmaceutical analytical development scientists
Rising to the Challenge of Biologic Drug Formulation

As biologics continue to push boundaries, the industry needs to take a holistic approach to formulation to ensure success.

FELICITY THOMAS

Over the coming years, the growth in the biologics market is projected to be rapid, reaching US$580.5 billion by 2026 (1). This growth is partly being attributed to an expansion in product portfolios, which is reflected in the higher number of biologics that are being approved by regulatory bodies globally (2).

“Medicine has experienced a revolution since recombinant DNA technologies moved from novel therapies in the mid-1980s to mainstream in recent times. The number of biologics gaining approval for an orphan indication has climbed to more than 50% in the current decade,” confirms Victoria Morgan, biologics marketing director, West Pharmaceutical Services. “Last year, 2018, was a record-setting year for new-molecular entity (NME) approvals by FDA, 59 versus 46 in 2017. More than half (58%) of NME approvals were for orphan drugs (patient population less than 200,000 in the United States) 17 of which were biologic NMEs.”

According to Peter Ferguson, global market manager for biopharma at Roquette, the past decade has witnessed a marked shift in the pharmaceutical industry. “Companies traditionally seen as ‘small molecule’ have pivoted their emphasis and pipelines towards biologics,” he says.

Currently, there is a wide range of modalities within the biopharmaceutical industry, Ferguson explains, with the repertoire of biologics now spanning monoclonal antibodies (mAbs), fusion proteins, and emerging areas such as cell and gene therapies. “Of all therapies classified as biologics, mAbs stand out far above the rest in terms of prominence,” he continues. “Representing approximately 50% of the market (well above the next category, vaccines) mAbs are not only the most commonly marketed biologic today, but if we look at pipelines, where there are nearly 4000 mAbs in development, the future of biopharma looks set to be dominated by this class of medicines.”

FORMULATION CHALLENGES

Poorly formulated drugs can have a significant impact on a development program, and if poorly formulated candidate drugs progress to the clinical trial stage, developers may be looking at wasted resources and erroneous data sets, stresses Ferguson. “This [concern] further exemplifies why formulation optimiz-
tion and pre-formulation activities are so important to delivering a successful program,” he says.

Regarding biologics in particular, the challenges associated with formulation, such as aggregation and degradation, must be extensively considered as these could have a severe impact on patient safety. “If an aggregated biologic is injected into a patient, there is a high chance of induced immunogenicity occurring,” continues Ferguson. “The impact of this [reaction] will be uncomfortable for the patient, but more importantly, will lead to the reduction in the therapeutic effects of the medicine. For a patient suffering with a life-threatening disease, such as cancer, a lack of efficacy in their treatment could be fatal.”

Morgan concurs that an extensive series of pre-formulation checks are imperative to ensure that developers avoid formulating an unstable, non-viable product (3). “Developers must determine whether the injectable biologic will break down within the intended formulation or the manufacturing process,” she says. “The drug must be thermally stable, possibly resistant to oxidation, and tolerate variations in light and other environmental stresses placed on it during manufacturing and packaging. Assessment of any residual solvents or other chemicals remaining after bulk preparation of the biologic will need to be accounted for in the formulation and manufacturing process. Finally, the solubility of the biologic must be assessed, to ensure that the formulation will result in high bioavailability without degrading or otherwise damaging the biologic itself. Ideal formulation conditions are then set, which may include the introduction of excipients, specific parameters that must be maintained during manufacturing, and/or the presence of vacuum during certain steps.”

“From speaking to formulators across the industry, preventing and reducing the level of aggregation is what we see as the critical issue facing biologic formulators in the market,” notes Ferguson. “This issue affects most biologic drugs, in particular monoclonal antibodies. It is not easily solved, with further challenges created due to the varied nature and three-dimensional structure of different biologics, as well as a limited number of approved excipients available on the market.” Specifically approaching this issue, Roquette has introduced a hydroxypropyl modified betacyclodextrin excipient (KLEPTOSE BioPharma), which was originally used in the small-molecule arena, Ferguson reveals.

**LIMITATIONS OF DELIVERY**

The mechanics of administration is also an important consideration for formulators. The increasing trend for subcutaneous formulations to be developed for high-dose drugs raises specific challenges, explains Morgan.

“The greatest challenge associated with the delivery of biologics lies in the limited delivery mechanisms available,” confirms Ferguson. “As most biologics are proteins, their chemistry makes them unsuitable for oral administration, due to the hydrolysis and degradation that would occur. If it were possible to formulate biologics into oral dosage forms, you would see a significant reduction in their total delivery cost.”

In agreement, Morgan explains that the complexity of biologics, compared with small-molecule drugs, has meant that the oral administration route has not been mastered. “There is enzymatic and pH-dependent degradation of drugs in the stomach and intestines,” she says. “Low permeability of epithelial cells that line the gastrointestinal tract means that proteins and peptides typically have extremely low bioavailability, in the range of around 0–2%, when taken by mouth.”

The size of biologics presents further delivery challenges. Molecular weights that can reach 150,000 Da, compared to a few thousand usually encountered with small-molecules, give rise to viscosity issues, emphasizes Ferguson. “The administration preference for high-viscosity formulations tends to be intravenous, which is a costly option, requiring clinicians and trained medical professionals to deliver the treatment,” he says.

However, Morgan notes that if it is possible to formulate the biologic to within the traditional <1 mL space, maintaining stability in liquid form, and with a reasonable viscosity, an auto-injector may be a suitable option for a combination product. However, if there is any deviation from the standard formulation parameters, then different technology for delivery is required. Morgan points out the example of Repatha (Amgen) in combination with the SmartDose wearable device (West Pharma Services).

“Bringing biologic combination products to market has numerous potential pitfalls, however,” she says. “One must ensure the right analytical methods are in place; have a repeatable, controlled manufacturing process; manage poor yields; test compatibility of drug with device; design an ideal device through human factors; and navigate successful clinical trials, all whilst regulating and testing to the appropriate regulatory agency expectations. Navigate these challenges well and you have a robust product and process.”

**ADDRESSING CHALLENGES**

Fundamental challenges affecting biologics may be addressed during the formulation stage. During formulation, many of the critical quality attributes and parameters of the drug product are defined, Ferguson explains. He notes that for aggregation, selecting the correct and optimum excipients is of paramount importance. However, the ability to be able to perform this task is dependent upon the tools the formulator has available to them.

“The area of pre-formulation stands out as an underutilized area of formulation optimization,” Ferguson continues. “I often ask those working in drug discovery how many lead candidates never make it through to trials simply due to a lack of screening robustness. The answer seems clear—potentially a lot. Often separated both organizationally and physically, groups working within formulation refer to an issue termed a ‘silo’ mentality within research and development. Uniting and harmonizing...
these different disciplines could bring numerous benefits to big pharma during the development of drug products.”

In Morgan’s opinion, both formulation and delivery device technologies can be employed to improve the overall patient experience. She says that formulating drugs to higher concentrations and using higher volume delivery systems can reduce dosing frequency, and using delivery systems that enable administration in the home setting can benefit the end user and potentially reduce healthcare expenses.

“Formulating drugs that can be self-administered by the patient has progressed the treatment and compliance of disease states such as rheumatoid arthritis and diabetes,” she adds. “The fundamental shift in this field has been the move to subcutaneous delivery rather than intravenous or infusion.”

Subcutaneous delivery is challenging, however, and requires formulators to balance the pharmacological needs of the drug with the tolerability of the patient. Potential solutions available include increasing the dose concentration or increasing the dose volume, Morgan further explains.

“Upstream we see challenges as these increased viscosities and volumes may not be amenable to existing fill/finish processes,” she adds. “Concentration to the necessary level in the final product may not be possible for all products because, in many cases, upstream purification and manufacturing processes may limit the maximum concentration for the final drug product more than delivery and fill/finish process concerns.”

Furthermore, limitations to the concentration can result from the drug-product properties, such as pH and osmolality, and the use of certain excipients. “Certain emerging formulation technologies, including the use of non-aqueous solutions, have shown promise towards mitigating such concerns, but are awaiting regulatory approval,” Morgan says.

Subcutaneous delivery is still causing concern in the industry, with difficulties encountered in the patient’s ability to tolerate rapid injection with the larger dose volumes. “However, the launch of ENHANZE (Halozyme) drug delivery technology has potentially turned that argument on its head,” Morgan notes. “Based on a patented recombinant human hyaluronidase enzyme, the technology enables some biologics that are administered intravenously to potentially be delivered subcutaneously, providing a better experience for patients and increasing health system efficiency by reducing administration time, injection pain, and infusion site reactions.”

Furthermore, she emphasizes the importance of wearable drug delivery devices in solving the issues surrounding larger volume doses. “A wearable allows longer dosing times, patient comfort and convenience; even allowing home administration, which opens up historically limiting parameters for formulators,” Morgan says.

LOOKING TO THE FUTURE

“When I look to the future of the biopharmaceutical industry, I see two main agents of change within the next 10 years: advancements and adoption of innovative manufacturing techniques and the rise of advanced therapy medicinal products (ATMPs),” says Ferguson.

In his view, traditional manufacturing techniques for biologics, which use stainless steel technology, will need to adapt to the changing targets for drug developers—narrower patient populations and more focus on specific disease categories. “The implication here is that manufacturing techniques will need to mirror the required flexibility and productivity increase required,” he says. “Single-use manufacturing techniques currently represent a small proportion of the installed biopharmaceutical capacity. Looking forward, I see a fundamental shift in the approach taken to the manufacture of biologics—one only has to look at plants currently under construction, of which 25–50% use single-use technology, to see the fundamental shift that is taking place.”

Morgan also touches upon manufacturing as an element she believes will witness change in the near future. “As biosimilar competition increases and pressure for biologics manufacturing costs to reduce, the number of approved biologics will continue to increase,” she explains. “We will see more outcome-based pricing as funders are under ever increasing pressure to stretch their funds.”

In terms of modality, Ferguson states that even though he believes mAbs will continue to dominate the biologics market into the future, there will be emerging areas, such as cell and gene therapy, that are set to play an increasingly important role. “The result that can be obtained with these therapies is outstanding, something of which the wider industry is starting to take note,” he says. “Formulations for these treatments will pose new challenges and significant benefits to patients. The stability and efficacy challenges confronting a formulation scientist in traditional biologics will not be the same for these advanced therapies.”

One trend that is being witnessed across the industry is that of a patient-centric approach to formulation. “Developers need to look beyond the formulation of a stable drug all the way to patient compliance. How will the patient receive the dose, in what setting, and with what level of pain are all factors which should be considered from early development stages,” Morgan summarizes. “As biologics continue to push the boundaries of what was historically possible, use of delivery devices to allow patients to successfully comply with stated dosing regimens is becoming widespread.”

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Visible particle contaminants can occur throughout the development and manufacturing of biologic drugs and can bring your process to a screeching halt. These contaminants cover a range of materials that may need to be identified including organics, inorganics and metals that can come from numerous sources including the protein formulation, storage containers, laboratory supplies, personnel, finishing/filling and manufacturing equipment. In this webcast, our speaker Andy Norriss from Genentech will discuss a method and the benefits of directly identifying metal particles in lyophilization cakes using microscopy-based laser-induced breakdown spectroscopy (LIBS) with the Hound system. Direct identification decreases the time to get answers and makes it possible to quickly track down the source of contamination.

**KEY LEARNING OBJECTIVES:**

- How to directly identify particles in lyophilization cakes
- The benefits of direct analysis with Laser-Induced Breakdown Spectroscopy (LIBS)
- How combined spectroscopic and morphology characterization with Hound can be used for root cause particle ID

**WHO SHOULD ATTEND:**

- Scientists
- Lab Managers
- Directors
- Quality Control
Reinventing the Biomanufacturing Wheel

To achieve further cost reductions in biosimilar manufacturing, a move away from traditional models is necessary.

FELICITY THOMAS

It is well known that numerous branded biologics are facing patent expiration before 2020, which is expected to lead to a continued increase in the numbers of biosimilars in development. As has been reported, European growth within the biosimilars market is accelerating rapidly while in other regions, such as the United States, progress has been slow (1), which has been attributed to regulatory frameworks (2) and a growing acceptance in Europe of biosimilars’ interchangeability with innovator drugs.

Cost represents an important aspect of the biosimilar sector. The biological copies of patented therapies can potentially offer patients a much more affordable treatment avenue, however, despite the positive cost impact that was anticipated to be brought on by biosimilars, there is increasing pressure on the market to be more competitive and offer further discounts on prices (1).

Belgian technology innovation company, Univercells, has taken the mission of making biologics affordable and available to all. The execution of this mission is critical in low- and middle-income countries (LMICs) where the current supply of these molecules is reliant on importation. “The advent of biosimilars was estimated to have a positive impact on accessibility by reducing selling prices by 30–40%,” explains Tânia Pereira Chilima, product manager at Univercells. “Yet, more significant price reductions are still required in order to ensure that these molecules are accessible to all of those in need. Hence, in order to reduce selling prices while maintaining high margins, cost-of-goods (CoG) reductions through process optimization are required.”

THINKING OUTSIDE THE BIOMANUFACTURING BOX

“The traditional manufacturing model for biologics relies on economies of scale to achieve cost-effectiveness,” Pereira Chilima says. “This model requires very large and expensive facilities producing tonnes of product yearly.”

However, for niche disease areas, the benefits of economies of scale are minimized as the annual throughput is reduced and hence the impact of capital investment is magnified, increasing the overall CoG, she explains. “Additional cost pressure points include labor costs and quality assurance costs, which do not necessarily decrease with scale, and hence become significant as a proportional of the total CoG when considering the low...
processing volumes required for niche diseases,” she adds.

A potential strategy to reduce CoG in biomanufacturing is the implementation of ‘smart facilities’. “Smart facilities can provide platform processes for cost-effective and low footprint manufacture of biologics with low capital investment requirement,” Pereira Chilima notes. The Nevoline offered by Univercells is an example of a smart facility. This ‘smart facility’ features a low footprint fixed-bed bioreactor with high surface area per unit volume, which operates in a perfusion mode in order to achieve high cell densities. Moreover, chaining principles were employed so as to enable an integrated and continuous upstream and downstream processing.

**A NEED TO MOVE AWAY FROM THE CLASSICAL MODEL**

“We need to reinvent the way we think about biologics manufacturing and move from the classical centralized stainless-steel facility model into innovative facility concepts, which allow for cost-effectiveness to be achieved even at the smaller scales characteristic of niche disease areas,” emphasizes Pereira Chilima. “Such facility concepts can be achieved through the implementation of manufacturing platforms that adopt the principles of chaining and intensification previously applied in the chemical engineering industry, in order to reduce footprint and capital investment. Moreover, coupling these principles with automation will further decrease the CoG through labor cost reductions.”

Through additional projects, Pereira Chilima notes that Univercells is looking to develop and deploy complete turnkey solutions that will enable low-cost and low-capital investment manufacture of biosimilars in LMICs. “These solutions will include the transfer of biological material, equipment, processes protocols, clinical documentation among other items” she says. “Moreover, the tech transfer activities and training of a local workforce will enable partners to build a strong knowledge base and be rapidly autonomous for the sustainable production of affordable biotherapeutics.”

“Global health is everyone’s responsibility as it is key for a good quality of life,” Pereira Chilima concludes, “This is even more crucial when it comes to immunization. When it comes to these vaccine products, our technology can ensure adequate availability to the population irrespective of geographic location.”

**REFERENCES**


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**Continuous bioprocessing of vaccines**

Europe is the leading region in vaccine production (1); however, if faced with a new epidemic, traditional vaccine infrastructures may struggle to cope with urgent capacity requirements. The Univercells’ Nevoline biomanufacturing platform—initially developed through a grant from the Bill and Melinda Gates Foundation (2)—has enabled a five-fold cost reduction in the manufacture of a live-attenuated polio vaccine.

“The system consists of a self-contained, single-use, modular, and flexible platform, which incorporates principles of automated and continuous bioprocessing,” says Tania Pereira Chilima, product manager at Univercells. “At its core lies the scale-X bioreactor, a fixed-bed bioreactor which is available on a range of configurations and provides up to 600 m² of area for cell growth within a 50-L bioreactor. In combination, the systems are capable of producing more than half a million doses of trivalent sIPV per batch.”

Additionally, this ‘smart facility’ concept can be applied to other vaccines and biologic molecules, Pereira Chilima confirms. “We are working on different applications for this facility concept, including its use in the production of affordable and readily available human and veterinary vaccines,” she says. “The platform can also be used to bridge the gaps in viral vector supply in cell and gene therapy. Furthermore, this facility concept can be employed in addressing pricing and availability challenges in the supply of monoclonal antibodies, such as Humira, a trend affecting countries worldwide.”

As part of the Gates Foundation grant to transfer the Nevoline platform along with sIPV process, clinical results, and so on, Univercells is also working on a Global Access Commitments Agreement so that the platform can be implemented in countries in need (3).

**References**


What’s New in Downstream Processing

The latest advances in downstream processing include remote monitoring, membrane chromatography technology, single-use sensors, and new uses of data analytics.

Tecnological advancements for downstream operations are crucial for maintaining efficiency and driving innovation in biomanufacturing. The following products and developments hold promise for improving the risks in this area of bioprocessing.

**UPDATED CLINICAL WATER PURIFICATION SYSTEM**
The Milli-Q CLX 7000 clinical water purification system from MilliporeSigma has been updated with a new cloud-based, remote lab water service and monitoring capability (1). The Milli-Q Connect online service portal provides digital access to water and system data, allowing users to monitor lab performance remotely and securely.

The Milli-Q Connect system turns passive data into active, actionable information that is available remotely. This process streamlines the production of quality reports, which can be produced in minutes, according to the company.

Other benefits include:

- Immediate and customized notifications, with remote access and control of the water system available from a secure online portal
- Remote diagnostics, and potentially repair, available directly through web-based portal
- Automatic data backup and rapid retrieval via Milli-Q Connect platform simplifies audit preparation and lab accreditation.

“Scientists have come to expect the same instant connectivity in their lab as they experience in their personal lives,” said Jean-Charles Wirth, head of Applied Solutions at MilliporeSigma, in a March 18, 2019 company press release. “This Internet-of-Things technology gives our customers accessibility to view real-time system information, customized notifications, and rapid online diagnostics, whether they are at the lab or at home.”

**MEMBRANE CHROMATOGRAPHY SYSTEMS IN DEVELOPMENT**
Biopharmaceutical supplier Sartorius Stedim Biotech (SSB) and Novasep, a provider of molecule production
and purification services, have entered into a collaboration in which the companies will develop membrane chromatography systems using Novasep’s BioSC platform and SSB’s single-use technology (2).

According to SSB, systems that are currently on the market are designed for resins, but do not take full advantage of membrane chromatography capabilities. Optimally run membrane chromatography processes will provide an efficient alternative to batch and continuous resin-based chromatography, resulting in higher productivity, smaller-scale operations, and increased robustness, as stated by SBB in a March 5, 2019 press release.

Novasep specializes in the design, manufacture and control of resin-based batch and continuous chromatography systems. The company’s BioSC platform is a low-pressure continuous chromatography solution for the purification of monoclonal antibodies, blood fractions, and other biologics. The platform is adaptable, with operations from one column up to six columns in batch, parallel batch, continuous chromatography, or continuous process; Novasep states that the platform can easily switch from batch to continuous, has a reduction of resin and buffer by up to 75%, and increased productivity by two- to six-fold.

PARTNERSHIP TO ENHANCE SINGLE-USE SENSORS

Pall Corporation, a filtration, separation, and purification solutions provider, has partnered with sensor technology provider Broadley-James Corporation to integrate and distribute Broadley-James’ advanced single-use probe and flow cell pH sensors (3). The sensors have both upstream and downstream operation applications and will be integrated into Pall Biotech’s single-use technologies, as well as other commercially available bioprocessing platforms.

The single-use pH sensors leverage glass electrochemical technology, which according to Pall, is the only method that meets international standards for pH measurement. The design includes a calibrated buffer storage environment for the sensor to eliminate previous constraints during pre-integration of glass pH sensors into consumables. Users will be able to operate in closed systems without sacrificing performance.

The Broadley-James single-use probe and flow cell pH sensors are currently in beta testing and will be available exclusively through Pall Biotech once launched. Parallel technical and process development support is also available to aid product use.

“Customers currently rely on calibration data gathered before the sensor is sterilized, which can affect the measurement accuracy,” said Robert Garrah, vice-president at Broadley-James, in a March 11, 2019 press release. “Our patent-pending new storage solution design features a known pH buffer, enabling robust pre-use calibration. By pairing trusted technology with cutting-edge design, we are able to offer the best balance of risk reduction and performance.”

DIGITAL DATA EXCHANGE PROGRAM MAY OFFER REDUCED RAW MATERIAL VARIABILITY

GE Healthcare and Amgen have established a digital data exchange collaboration program that will include advanced data analytics to increase the understanding of the relationship between raw material variability and process performance during the manufacture of biologic medicines (4). The companies will be installing a seamless connection for data transfer between GE Healthcare raw material manufacturing sites and Amgen’s process development center in Cambridge, MA.

“This project is a perfect example of the type of collaboration we want to drive together with the biopharma industry, pushing the boundaries of manufacturing efficiency and performance reliability even further,” said Olivier Loeillot, general manager, BioProcess at GE Healthcare Life Sciences, in a March 11, 2019 press release. “The data exchange capabilities that we are introducing can have a huge positive impact on the biomanufacturing operations, and this is only the beginning of our digital journey.”

According to GE, the ability to detect and monitor raw material variability through data integration will be an important step to ensuring consistent and predictable biomanufacturing performance. Data insights can be used to drive process and product improvements and reduce the potential for supply disruptions.

“We know that slight changes in raw materials can have a significant impact on product attributes of biotechnology medicines,” said Rohini Deshpande, vice-president, Attribute Sciences at Amgen, in the press release. “At Amgen, we seek to understand our end-to-end supply chain, from raw materials to finished products. By analyzing data directly from the manufacturing site for raw materials, we can have a better understanding of the effect of variations in raw materials on our products.”

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Osmolality is easy to measure and serves as a robust critical processing parameter in bioprocessing.

Osmolality has long been viewed as a release specification for final drug formulations. However, osmolality could and should be implemented for many process checkpoints throughout the bioprocessing workflow. For instance, the health and yield of upstream cell culture can be effectively monitored with osmolality testing. In downstream processing, osmolality can serve as a sensitive and reliable process control for buffer exchange as well as for the monitoring of protein purification. *BioPharm International* recently sat down with Kristeena Wright, PhD, Application Scientist at Advanced Instruments, to discuss the value of osmolality testing and how biopharmaceutical manufacturers could benefit from increasing its implementation.

**BioPharm International:** What value does osmolality testing bring to bioprocessing?

**Wright:** Osmolality is the number of milliosmoles of a solute per kilogram of solvent. In bioprocessing, the solvent is typically water. Osmolality is a well-established measure of solute concentration and a robust, cost-effective method of process control. Although it is a standard measurement in upstream processing and final formulation, osmolality is underutilized in downstream processing. Advanced Instruments recognizes the value of implementing osmolality testing throughout the bioprocessing workflow.

**BioPharm International:** What specific value does osmolality have in an upstream processing environment?

**Wright:** The osmolality of cell media or cell feed is a critical parameter to ensure cell viability and growth, both during media preparation and within a cell culture system. This ensures optimal titer and operational reproducibility. For many cell lines, it is ideal to maintain the osmolality of the cell culture broth such that it approximates the osmolality of the cell line’s natural environment. That is why it is critical to check osmolality after the addition of saline solutions, hormones, nutrients, and so on.

**BioPharm International:** Are there as many potential applications of osmolality within downstream processing as there are with upstream processing?

**Wright:** Yes, if not more. Osmolality could and should be implemented at many process checkpoints throughout the...
downstream processing workflow. Buffers must be carefully monitored and controlled to ensure protein compatibility and efficient purification. Osmolality can serve as a sensitive and reliable process control for buffer exchange as well as purification monitoring.

**BioPharm International: What are some examples of the value of osmolality in downstream processing?**

**Wright:** We have heard anecdotal examples of processing errors and batch failures that may have been prevented with the implementation of osmolality testing. Investigations have revealed problems with buffers that may have been detected if osmolality had been tested throughout the process. Advanced Instruments recently completed a study to better understand the value of osmolality in measuring the concentration of some common downstream buffers. We worked with seven buffers and buffer components that have a variety of roles throughout downstream processing, including Tris, phosphate buffer, and citrate buffer. These solutions were prepared at a wide range of concentrations and tested for osmolality as well as the standard conductivity and pH. We found that, in some cases, osmolality provided a more sensitive and reliable measure of solute concentration compared with conductivity and pH. By sensitive, we mean that a deviation in concentration corresponds to a large change in osmolality because the instrument has a wide dynamic range. The reliability of osmolality in this study refers to the predictable trends that we saw across concentrations ranges. The study is detailed in a new Application Note, which can be found on our site.

**BioPharm International:** Are you suggesting that osmolality should replace the standard measurement of pH and conductivity during processing?

**Wright:** No, we realize that pH and conductivity are invaluable process controls. These parameters are also temperature and ionization dependent, however, which is not ideal for the characterization of all buffers and solutions. Osmolality, on the other hand, measures the total solute concentration and is relatively independent of environmental factors. Osmolality testing can provide independent but complementary information about solutions. Together, these parameters will help maintain control of the process, minimize errors, and ensure optimal product yield and quality.

**BioPharm International:** How can osmolality drive Quality by Design?

**Wright:** Quality by Design relies on operation-specific critical process parameters (CPPs). We know that osmolality is crucial to the survival and yield of cells in upstream processing. It could also serve as a robust critical process parameter in downstream processing. Osmolality is quick and simple to measure, and it provides unique information about the concentration of buffers and process intermediates. Ultimately, implementing this measurement method will also lead to fewer batch failures and higher cost savings.

“\n\nFor many cell lines, it is ideal to maintain the osmolality of the cell culture broth such that it approximates the osmolality of the cell line’s natural environment."
\n\n"For many cell lines, it is ideal to maintain the osmolality of the cell culture broth such that it approximates the osmolality of the cell line’s natural environment."
\n\nAdvanced Instruments is a global provider of scientific and analytical instruments for the biotech, clinical, and food-and-beverage industries. The company's innovations have helped organizations improve quality of results, achieve reliable outcomes, and increase workplace productivity. Advanced Instruments has a diverse portfolio of products, including freezing-point depression osmometers and their calibration standards and control solutions. Its gold-standard testing method provides the accuracy and precision needed to optimize bioprocesses and quality control programs.

To access the latest Application Note on osmolality testing of downstream buffers, visit www.aicompanies.com/dsp-appnote.

For more information, visit www.aicompanies.com
Cleaning Chromatography Resin Residues from Surfaces

Laboratory test methods evaluate cleaning agents and cleaning process design for non-dedicated chromatography columns systems.

ELIZABETH RIVERA AND DIJANA HADZISELIMOVIC

Liquid chromatography is used for separating materials in biopharmaceutical production, primarily for purifying proteins by separating product and impurities. The stationary phase in liquid chromatography uses fine, solid beads referred to as resins that are packed and held in a column by meshes. These particles can be physically or chemically modified to provide specificity to grab or repel molecules within mixtures.

REGENERATING RESINS

Chromatography resins are typically dedicated to a single product. They can be either disposed of or cleaned to an acceptable level to render them suitable for use in subsequent cycles. The decision to reuse or dispose of resins is primarily driven by a cost analysis (1–2). For that reason, biopharmaceutical manufacturers reuse chromatography resins multiple times to make them affordable for inclusion in downstream processes (3–4). Regenerating or “cleaning” the resin is necessary for this purpose. The process consists of removing residual proteins and impurities from the resin while inside the column. Regeneration may be done after every loading cycle or after a few loading cycles.

Once impurities bind irreversibly, accumulating over time and consequently deteriorating the chromatography process performance, the resin needs to be regenerated to restore process performance and to minimize the risk of carryover (5). Caustic solutions at concentrations between 0.1–2 M were reported to be effective at regenerating most types of resins (6–7). Caustic solutions have also been effective at inactivating most viruses, bacteria, yeasts, fungi, and endotoxins and can be easily detected, removed, and disposed of. Other publications show that resins are effectively cleaned and sanitized with acidic solutions such as benzyl alcohol (8). Many times, the regenerating solution is used to store the cleaned resin for a prolonged time when not in use either in the column or in a separate storage vessel (7).

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CLEANING RESIN RESIDUE

Regeneration of resin as described above has been well documented. Cleaning of the resin residue itself specifically from process equipment surfaces has not been widely addressed. While the resin packing is typically dedicated to one product, the chromatography column system may be employed for multiple products. After cleaning, the resins may be placed in another vessel for short or long-term storage. Other equipment that may have indirect contact with the resin are the slurry and packing tanks, and smaller parts such as hoses and valves. All these items must also be free from resin residues prior to use on the next product batch.

Most cleaning validation approaches are centered around removing either protein or process impurities from surfaces, and not on the resin residue itself. Residues from a chromatography resin are different from a protein in multiple ways. For example, the resin size may be more than 3000 times larger than a protein. As a general rule, the longer and more complex a molecule is, the harder it is to clean. Also, proteins in general degrade in the presence of caustic solutions while most resins have good chemical compatibility. The chemical compatibility allows resins to be stored in caustic solutions, which can be beneficial due to their antimicrobial properties. Lastly, carbon content is variable (but mostly negligible) from resin to resin compared to proteins.

For removing resin residues, the most commonly used solutions are sodium hydroxide (NaOH) and sodium chloride (NaCl), or even hot water for injection (WFI). Nonetheless, the physical and chemical properties of resins may be quite different from other residues of typical cell–culture processes. Cleanability studies should be conducted to demonstrate the suitability of these commodities for cleaning non-dedicated chromatography columns and to ensure that there is no cross-contamination between resins used for previously manufactured product into the next product. Cross-contamination concerns may also include microbial or allergen risks. This paper provides a case study that evaluates the cleaning efficacy of NaOH and formulated cleaning agents against resin residues. A general recommendation for cleaning resin residues is provided.

Defining the design inputs and outputs for cleaning resins is an important part of the cleaning process design. Cleaning parameters for a wash step may include the cleaning agent, concentration, temperature, time, cleaning method, water quality, and environmental factors (9). Cleaning agents should be selected based on laboratory studies that simulate the soil condition and cleaning method used as well as performing a supplier qualification and technical support review. A good experimental design must be used to identify the parameters that have a significant impact on cleaning within a selected range (10–11).

LABORATORY TEST MODEL

Manufacturing process parameters, such as dirty hold time, materials of construction, and soil conditions should be well understood before designing the cleaning process. Understanding all these factors will lead to a better design of the laboratory test model. As seen in Figure 1, laboratory testing can include coating of the soil onto a stainless coupon and conditioning it in an oven for a specified time and temperature (12). After the coupon is conditioned, it can be cleaned by several different cleaning methods.

In a laboratory set up, agitated immersion may be conducted as a standard for cleanability studies. Agitated immersion consists of the cleaning agent solution mixed in a beaker and equilibrated to temperature and concentration. The coupon is conditioned with the resin soil and placed into a beaker containing the cleaning agent. At select intervals, the coupon is visually inspected and either returned to the cleaning agent for additional time or evaluated for cleanliness using analytical methods, as needed. This cleaning method is generally considered worst-case when compared with clean-in-place systems because minimal action is employed.

The following discussion centers on the cleanability of various resins used and submitted by a biopharmaceutical company located in the United States. The biopharmaceutical site had concerns about the suitability of its current cleaning procedure using a commodity chemical (NaOH) for removing resin residues from the chromatography column and other ancillary equipment.

CLEANABILITY CASE STUDY

Laboratory evaluation and conditions

A total of seven different resins were evaluated: Q Sepharose XL Resin (GE Healthcare Life Sciences), SP Sepharose FF Resin (GE Healthcare Life Sciences), Butyl Sepharose HP Resin (GE Healthcare Lifesciences), ProSep vA Ultra Resin (MilliporeSigma), MabSelect SuRe Resin (GE Healthcare LifeSciences), Ceramic Hydroxyapatite Resin (Bio-Rad Laboratories), and Poros XS Resin (Thermo Fisher Scientific).

Figure 1. Laboratory studies for cleaning evaluation.
The detailed test procedure is described in Table I and samples of resin-coated coupons are shown in Figure 2. The critical parameters investigated during the cleaning process design testing included varying wash times, cleaning chemistries, cleaning agent concentration, and temperature (see Table II). The dirty hold time (air-dried for 48 hours and baked at 121 °C for one hour), cleaning action (low agitation, spray wash, and cascading flow), water quality (de-ionized), and surface characteristics (304 stainless steel with a 2B finish) were unchanged for this study. A coupon was considered clean if it was visually clean, water break free, and if the difference between its pre-coating weight and post-cleaning weight was not detectable (0.0 mg of residue) (13). Refer to Table II for a sample summary of study details.

### Results and discussion
Sodium hydroxide (NaOH) is commonly adopted as the cleaning agent for removing resin residues from the surface. This cleaning agent primarily uses the mechanism of solubility of the solute in NaOH at the temperature cleaned. When a formulated cleaning agent is used, the cleaning mechanisms to remove the residue from the surface may include solubility in an aqueous solution, wetting, emulsification, dispersion, chelation, and hydrolysis (14). These additional cleaning mechanisms are important in removing water insoluble residues from the surface. A formulated cleaner containing potassium hydroxide was successful in cleaning resin residues using 1% v/v cleaning solution at ambient temperature up to 60 °C depending on drying hold times of the coupons. Coated coupons, air-dried at ambient temperature for 48 hours, were easy to clean using the formulated cleaner (data results not shown). When coated coupons were baked at 121 °C for one hour, higher temperatures (45 °C to 60 °C) were required to clean the residues. Sodium hydroxide was not successful in cleaning the resins using elevated temperatures and longer cleaning times. Deionized (DI) water and a formulated acid cleaner containing phosphoric acid also were not able to clean the residues using different cleaning parameters (refer to Table II). Cleaning results were confirmed by spray wash and cascading flow (data not shown).

### CONCLUSION
A cleaning validation and changeover approach should consider resin removal from process equipment. The type of resin, temperature, and cleaning agent selection had a significant impact on cleanability of the stainless-steel coupons used in the study to evaluate the performance of various cleaning agents in removing residues of common chromatography resin residues from a stainless-steel surface. A potassium hydroxide-based formulated cleaning agent at 1% v/v up to 60 °C for up to 60 minutes was effective in cleaning the residues. Even though NaOH is widely used in the biopharmaceutical industry for cleaning resins, it did not perform as well as the potassium hydroxide-based formulated cleaning agent within this study. For some resins, a phosphoric acid-based cleaner was also effective in cleaning the residue and may be added as a secondary step particularly for mineral-based resins.

### Table I. Laboratory test procedure.

<table>
<thead>
<tr>
<th>Step</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dried and cleaned 304-grade stainless steel coupons (7.5 x 15 cm size) were weighed on an analytical balance (±0.1 mg) to obtain the pre-coating weight.</td>
</tr>
<tr>
<td>2</td>
<td>Coupons were coated with 3–5 mL of the sample. The amount of residue per surface area was controlled and recorded (see Figure 2).</td>
</tr>
<tr>
<td>3</td>
<td>The coated coupons were air-dried at ambient temperature for 48 hours or baked at 121 °C for one hour.</td>
</tr>
<tr>
<td>4</td>
<td>The coated coupons were weighed on an analytical balance to determine the pre-cleaning weight.</td>
</tr>
<tr>
<td>5</td>
<td>Each coupon was cleaned by agitated immersion, spray wash, or cascading flow.</td>
</tr>
<tr>
<td>6</td>
<td>Each coupon was removed and visually observed for cleanliness.</td>
</tr>
<tr>
<td>7</td>
<td>Each side of the coupon was rinsed with tap water for 10 seconds at a flow rate of 2 L/min.</td>
</tr>
<tr>
<td>8</td>
<td>Each side of coupon was rinsed with deionized water and examined for a water break-free surface.</td>
</tr>
<tr>
<td>9</td>
<td>Coupons were dried and then weighed on an analytical balance to determine the post-cleaning weights.</td>
</tr>
</tbody>
</table>
Table II. Summary of testing conditions and results for the agitated immersion cleaning method. The coated coupon was immersed in a 1500-mL beaker filled with a cleaning solution, and the solution was agitated at a mild speed using a magnetic stirrer. Formulated H₃PO₄ is formulated cleaner containing phosphoric acid, and Formulated KOH is formulated cleaner containing potassium hydroxide. Concentration of 0.2 M is equivalent to 2 g/L.

<table>
<thead>
<tr>
<th>Resin (baked on at 121 °C for 1 hour)</th>
<th>Temp (°C)</th>
<th>Conc (% v/v)</th>
<th>Cleaner</th>
<th>Wash time (min)</th>
<th>Visual observation</th>
<th>Water break free (WBF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q Sepharose XL Resin</td>
<td>60</td>
<td>N/A</td>
<td>Deionized water (DI)</td>
<td>60</td>
<td>Moderate</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.2 M</td>
<td>Sodium hydroxide (NaOH)</td>
<td>60</td>
<td>Moderate</td>
<td>Trace</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>Formulated H₃PO₄</td>
<td>60</td>
<td>Moderate</td>
<td>Trace</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>Formulated KOH</td>
<td>30</td>
<td>Visually clean</td>
<td>YES</td>
</tr>
<tr>
<td>SP Sepharose FF Resin</td>
<td>60</td>
<td>N/A</td>
<td>DI</td>
<td>60</td>
<td>Moderate</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.2 M</td>
<td>NaOH</td>
<td>60</td>
<td>Moderate</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>Formulated H₃PO₄</td>
<td>60</td>
<td>Moderate</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>1</td>
<td>Formulated KOH</td>
<td>15</td>
<td>Visually clean</td>
<td>YES</td>
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<tr>
<td>Butyl Sepharose HP Resin</td>
<td>60</td>
<td>N/A</td>
<td>DI</td>
<td>60</td>
<td>Moderate</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.2 M</td>
<td>NaOH</td>
<td>60</td>
<td>Moderate</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>Formulated H₃PO₄</td>
<td>60</td>
<td>Visually clean</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>1</td>
<td>Formulated KOH</td>
<td>30</td>
<td>Visually clean</td>
<td>YES</td>
</tr>
<tr>
<td>ProSep vA Ultra Resin</td>
<td>60</td>
<td>N/A</td>
<td>DI</td>
<td>60</td>
<td>Moderate</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.2 M</td>
<td>NaOH</td>
<td>60</td>
<td>Moderate</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>Formulated H₃PO₄</td>
<td>60</td>
<td>Visually clean</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>1</td>
<td>Formulated KOH</td>
<td>15</td>
<td>Visually clean</td>
<td>YES</td>
</tr>
<tr>
<td>MabSelect SuRe</td>
<td>60</td>
<td>N/A</td>
<td>DI</td>
<td>60</td>
<td>Moderate</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.2 M</td>
<td>NaOH</td>
<td>60</td>
<td>Moderate</td>
<td>Trace</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>Formulated H₃PO₄</td>
<td>60</td>
<td>Visible clean</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>Formulated KOH</td>
<td>30</td>
<td>Visually clean</td>
<td>YES</td>
</tr>
<tr>
<td>Ceramic HA Resin</td>
<td>60</td>
<td>N/A</td>
<td>DI</td>
<td>60</td>
<td>Moderate</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.2 M</td>
<td>NaOH</td>
<td>60</td>
<td>Moderate</td>
<td>Trace</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>Formulated H₃PO₄</td>
<td>60</td>
<td>Visible clean</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>1</td>
<td>Formulated KOH</td>
<td>60</td>
<td>Visible clean</td>
<td>YES</td>
</tr>
<tr>
<td>Poros XS</td>
<td>60</td>
<td>N/A</td>
<td>DI</td>
<td>60</td>
<td>Moderate</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.2 M</td>
<td>NaOH</td>
<td>60</td>
<td>Moderate</td>
<td>Trace</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>Formulated H₃PO₄</td>
<td>60</td>
<td>Visible clean</td>
<td>YES</td>
</tr>
</tbody>
</table>

REFERENCES
Changing Perceptions:
An Understanding of Lyophilization
Advancements

Technical advances in process understanding and control must be accompanied by a change in mindset.

FELICITY THOMAS

Since its introduction to the pharmaceutical industry in the 1940s, lyophilization (freeze-drying) has been a mainstay for manufacturers to stabilize products and ensure they are durable and safe for as long as possible. In recent times, lyophilization has experienced a surge in interest, which has been attributed to the rising proportion of biopharmaceuticals being developed and manufactured that are generally unstable in aqueous form (1).

A STABILIZING PROCESS
Essentially, lyophilization is the ability to remove water while maintaining chemical or biological function, explains T.N. Thompson, president, Millrock Technology. “It is a three-step process involving freezing, primary drying or sublimation, and secondary drying (sometimes referred to as desorption),” he continues. “Freezing is the most important step of the entire process. If the product is not frozen properly, then the primary drying process can be inefficient or impossible.”

“Ultimately, lyophilization is a stabilizing process that is used to preserve the long-term safety, strength, and quality of pharmaceutical products, especially for parenteral biologics,” confirms Alina Alexeenko, from Purdue University in Indiana, and co-director of the Advanced Lyophilization Technology Hub (LyoHUB)—an industry-led partnership aimed at advancing the science and technology of lyophilization.

Currently, there are an increasing number of biological drugs in development or being approved by regulatory bodies worldwide (2). “Many drugs are unstable in solution,” continues Elizabeth Topp of Purdue University, co-director of LyoHUB. “These drugs are often marketed in solid forms to preserve their potency and prolong their shelf-life. This is particularly true for biologics.”

It is this growth in biologics that has contributed to the rising importance for lyophilization, they specify. “Unlike other drying methods, lyophilization removes water in a relatively gentle way that helps to preserve the structure and
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KEY LEARNING OBJECTIVES

- TEM-based image analysis can identify and quantify the amount of detailed surface structures on viral particles
- Removal of impurities at each step of the virus purification can be monitored by using TEM-based image analysis
- Failure in viral particle packaging and loss of integrity can be quantified by TEM-based methods

WHO SHOULD ATTEND:

- Scientists, senior scientists, and department heads in analytics, formulation, process development, and biophysics engaged in vaccine, gene therapy, and oncolytic virotherapy

For questions contact Kristen Moore at kmoore@mmhgroup.com
activity of peptide and protein drugs,” says Topp.

“For biopharmaceuticals, the increasingly complex molecular formats are very unstable in solution,” agrees Sajal M. Patel, associate director, MedImmune. “Lyophilization offers a well-established process that can deliver stable products for parenteral delivery.”

**FUNDAMENTALLY UNCHANGED?**

The well-established process of lyophilization is considered by many to be both time- and cost-intensive, and has been described as fundamentally unchanged (3). However, according to some experts, these descriptions may not truly reflect the progress that has been made in the lyophilization process over the past few decades.

“The physics may not have changed but our knowledge of the process, equipment, and instrumentation has improved significantly,” Thompson stresses.

An improved understanding of the freeze-drying process has led to improvements in the equipment design, Thompson continues to explain. “One such improvement includes the refrigeration systems, which are now properly sized and far more reliable,” he says. “Others include condensers that can effectively handle high vapor loads, vapor port designs that don’t choke the vapor flow, sterilization methods for GMP processing, loading and unloading automation, and isolators, to name a few.”

Not only have there been advances in the instrumentation and control of the process, but also knowledge of the process itself has improved, Thompson adds. “Our understanding of the product critical temperature has improved, for example, which has enabled us to optimize the shelf temperature and chamber pressure to maintain the product just below its critical point while maximizing the sublimation rate,” he notes. “Also, the freezing methodology has changed. We now understand that the method of freezing affects the crystal structure in the product.”

Understanding of the drying process has also improved. Primary drying, for example, would periodically step up the shelf temperature over time in the past, which resulted in long drying cycles that were susceptible to failing. “We now know that the sublimation rate at the beginning of the cycle can be driven very fast, but as the dry layer builds up in the vial, the sublimation rate is reduced and the product temperature increases, so the shelf temperature needs to be reduced,” he adds. “So, today, it is not uncommon to have a high shelf temperature initially and then reduce it for the majority of the cycle, which reduces the primary drying time significantly.”

Knowledge of the vacuum level and its effect on the product temperature has also improved. “In the old days, many freeze dryers did not have a method for vacuum control, and often primary drying was attempted at pressures as low as 5 millitorr. It was believed that the lower the chamber pressure the better,” Thompson notes. “Today, we understand that the chamber pressure should typically be between 60 and 200 mT for the maximum sublimation rates and for proper process control.”

**TIME AND COST CONSIDERATIONS**

“The literature widely describes lyophilization as time-consuming and expensive,” says Patel. “However, both time and expense are relative. It may seem obvious to compare lyophilized drug products to liquid drug products; however, this is an inappropriate comparison as lyophilization is considered when solution stability is unacceptable.”

Because many biopharmaceutical products are unstable in solution, time and expense spent on lyophilization could be negligible when considering the total cost of manufacturing biological drugs, Patel explains.

“Regarding optimization of the lyophilization cycle time, there are several publications in the literature addressing this topic,” he adds. “Significant progress has been made over the past three decades in terms of heat and mass transfer understanding during the lyophilization process to allow development of the shortest possible lyophilization cycle without impacting product quality attributes. Recent publications (4) demonstrate the application of single-step drying (wherein primary and secondary drying is performed in a single step) that can significantly reduce the lyophilization cycle time.”

For Alexeenko, a key reason as to why lyophilization is time-consuming and expensive is that it is currently a batch process with open-loop controls. “An open-loop process is performed using a fixed and often quite conservative recipe,” they say. “Conversely, closed-loop processes use immediate feedback from process sensors.”

“Processing times for many existing freeze-dried products were developed when our process knowledge was limited, resulting in very long freeze-drying cycles, often lasting a week,” notes Thompson. “However, with our current knowledge of freezing and primary drying process dynamics, the processing times can be dramatically reduced—often to less than 24 hours.”

**INNOVATION IN LYOPHILIZATION**

Overall, industry’s goal for lyophilization is to be able to achieve high quality, lower cost, and more readily available lyophilized products, according to Alexeenko and Topp, who led the development of the Lyophilization Technology Roadmap (5), which was released by LyoHUB in September 2017.

“The roadmap, funded through a grant from the US National Institute of Standards and Technology, was the culmination of two years of workshops and meetings involving over 100 contributors who identified lyophilization needs in products, process, equipment, education, and regulatory interface,” they add. “It identifies two broad areas of effort needed to move toward improving lyophilization: advancing lyophilization technologies and tech-
niques and strengthening the industry foundation.”

Technical innovations will be required across all areas of lyophilization, including the lyophilized products, the lyophilization process, and the lyophilization equipment, they note. “The full implementation of these technical innovations will depend on a strong industry foundation, which will require that the interface between the industry and regulatory agencies be strengthened and that a well-trained workforce be developed and maintained.”

For Thompson, significant improvements to assist in the efficiency of lyophilization would come if closed-loop control was employed based on the product temperature rather than the shelf temperature. “Today, the control process is open loop—the shelf temperature is set and controlled and the chamber pressure is set and controlled, but no adjustments are made during the process based on the critical process parameters,” he says. “The semiconductor industry uses closed-loop control on all of their processes to maintain consistent quality levels. The pharmaceutical industry needs to begin to adopt the same type of process control to ensure quality and reduce processing times.”

CHALLENGES TO CONTROLLED NUCLEATION
A technique that has been discussed and researched for some time is that of controlled ice nucleation. However, uptake of this technique from a commercial standpoint has been slow. “When controlled nucleation was first introduced it was over-marketed as a methodology to reduce primary drying time,” states Thompson. Although it is a technique that is widely available in laboratory freeze dryers, he adds that there are certain roadblocks to its implementation within mainstream production.

“There have been significant advances in using controlled ice nucleation in research and development, with over 250 publications on controlled ice nucleation since 2010 (about half of them in the past three years). However, there is still a need for integration of ice nucleation technology in validated manufacturing processes,” agrees Alexeenko.

Patel also concurs with the challenge of availability of controlled ice nucleation at the production scale. “It’s difficult to modify existing freeze-dryers, and new facilities are reluctant to adopt the technology with the argument that controlled nucleation is ‘nice to have’ but not a ‘must have’, he says. “Controlled nucleation cannot be implemented in early development because there are not many manufacturing facilities that have controlled nucleation capability.”

“The major benefit for controlled nucleation is to produce a consistent ice formation across the batch at the beginning of the freezing cycle,” summarizes Thompson. “Consistency across the batch improves the quality of the finished product. I believe that the best way to justify implementation of controlled nucleation is to improve the quality and consistency of the finished product. If it also reduces process times, it is an added bonus.”

THE IMPORTANCE OF PAT
Experts agree that process analytical technology (PAT) is important in the advancement of lyophilization. “PAT is an integral part of the lyophilization process design, development, optimization, and scale-up,” emphasizes Patel. “The information gained about the process performance and the understanding of parameters that could potentially impact product quality are key to building quality within the product rather than testing quality at the end of the process.”

PAT is also vital for industry to achieve closed-loop control in lyophilization, notes Alexeenko. “Many new PAT solutions are being developed and applied now, especially for direct measurement of product temperature, in-situ measurement of lyophilization rate, and tracking non-aqueous solvents in complex formulations,” she adds.

Thompson, however, stresses that the definition of PAT needs to be clear. “PAT is a technology that provides direct measurement of the critical process parameters in real time for process monitoring and control,” he says. “Users need to understand that many of the PAT tools being offered by manufacturers provide information based on indirect measurements and calculations based on assumptions. Many of the tools provide ‘batch average’ information, which does not provide the resolution needed to understand the process variations across a batch of vials.”

AND WHAT ABOUT CAKE APPEARANCE?
A rather controversial topic that has been the subject of much debate over the years is that of cake appearance. “The common misunderstanding is that the end user demands a good look and feel for a lyophilized product or that in certain markets, pharmaceutical elegance is critical,” explains Patel. “However, there are no data to support any of these misunderstandings. On the contrary, some of the experiences shared within the industry suggests otherwise (6).”

In partial agreement, Thompson states that cake appearance is very subjective and in fact, a poor cake appearance is not an indicator of an improperly freeze-dried product or poor drug substance. “However, a doctor who takes a vial and is adding water before injection would be very concerned if the cake appeared to be collapsed. They cannot be sure whether the product was exposed to high temperatures or the seal on the vial was compromised,” he says. “New studies show that in some cases, product that has collapsed during freeze drying may result in more stable product that can be fully reconstituted (7). The challenge is whether the doctors in the field will trust the product.”

A CHANGE IN MINDSET IS NEEDED
“Our knowledge and understanding of lyophilization has evolved significantly...”
Leveraging Computational Models of Glycosylation for Biopharma QA

Close collaboration between academic and industrial groups is vital to ensuring glycosylation models are fit for deployment.

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Many of the highest-grossing protein therapeutics, including monoclonal antibodies (mAbs), Fc-fusion proteins (etanercept [Enbrel, Amgen/Pfizer] and aflibercept [Eylea, Bayer/Regeneron]), interferon gamma (IFN-γ), erythropoietin (EPO), and tissue plasminogen activator (tPA) contain complex carbohydrates (glycans) covalently bound to their peptide backbone (1). In turn, the presence and relative abundance of different glycan motifs (e.g., α-1,3 galactose, core fucosylation, and sialylation) are well-known to influence the safety, serum-half life (pharmacokinetics) and the therapeutic mechanisms (pharmacodynamics) of the aforementioned biopharmaceuticals (2). Glycosylation is also widely acknowledged as a major source of therapeutic protein heterogeneity (3), which is highlighted by work that found considerable glycosylation variation among different commercial lots of the same biopharmaceutical product (4).

Biopharmaceutical glycosylation variability is determined by manufacturing bioprocess conditions (1). Large-scale mammalian cell culture is used for the manufacture of all therapeutic glycoproteins (TGP), with Chinese hamster ovary (CHO) and murine myeloma (NS0 and Sp2/0) cell lines being the most-commonly used production platforms (5). During cell culture, even subtle variations in nutrient availability, dissolved oxygen, temperature, ammonia, and pH may impact the intracellular process of glycosylation (1,3) and yield product that cannot be administered to patients. Due to its bioprocess-associated variability and impact on safety, pharmacokinetics, and pharmacodynamics, glycosylation is widely regarded as a critical quality attribute (CQA) of TGP (1).

In the context of biopharmaceutical quality assurance, 21 mathematical models for protein glycosylation have been developed over the past decade. Although the strategies to mathematically describe the glycosylation process have been diverse, all models have demonstrated potential toward addressing one or more quality assurance (QA) issues associated with TGP manufacture. This review focuses on how different modeling strategies can be leveraged to aid in product QA across the different stages of biophar-
Approaches to mAb Charge Variant Characterization Using On-Line CEX-MS and Off-Line Analysis of CEX Purified Variants

ON-DEMAND WEBCAST  Aired April 17, 2019

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

EVENT OVERVIEW
The separation and analysis of monoclonal antibody charge variants is frequently performed during the discovery, development, and manufacture of innovative new biotherapeutics or biosimilars. It is well recognized that both capillary electrophoresis (e.g., capillary isoelectric focusing) and either cation-exchange chromatography (CEX) or anion-exchange chromatography (AEX) can be successfully used to generate reproducible, high-resolution separations. However, an understanding of the structural and functional differences between these charge variants is often required.

Using monoclonal antibody (mAb) protein as examples, this webinar will cover the principals of CEX charge-variant separations and some approaches to obtain information-rich data via on-line mass spectrometry (MS) detection; as well as the efficient isolation of charge variants using traditional non-volatile buffers, and their subsequent characterization using the evaluation of collected fractions.

Topics discussed in the webcast include the following:
- CEX for effective protein separations
- Challenges and concerns related to mAb charge-variant analysis
- Considerations using on-line MS detection of CEX separated mAbs
- Further characterization via traditional fraction collection approaches

Key Learning Objectives
- Review the factors that affect CEX of proteins
- Successful application of cation-exchange chromatography to mAb analysis
- Characterization of CEX separated mAb charge variants

Who Should Attend
- Biopharmaceutical scientists involved in drug discovery and development of mAbs and antibody-drug conjugates
- Biopharma companies
- Contract research organizations (CROs)
- Contract manufacturing organizations (CMOs)
- Universities/Research

Presenters
Samantha Ippoliti
Senior Scientist, Scientific Operations, Waters Corporation

Stephan Koza
Consulting Scientist, Scientific Operations, Waters Corporation

Moderator
Rita Peters
Editorial Director, BioPharm International

For questions contact Kristen Moore at KMoore@mmhgroup.com
maceutical product development and manufacture. Technical details on glycosylation models have been outlined elsewhere (6).

GLYCOXYLATION IMPACTS THE SAFETY AND EFFICACY OF PROTEIN THERAPEUTICS

The following individual glycosylation motifs that are known to influence the safety, pharmacokinetics, and pharmacodynamics of TGs are presented in Figure 1:

- Presence of high-mannose glycans, in particular, the five-mannose glycan (Man5), reduces the serum half-life of antibodies (7). Man5 may also enhance antibody-dependent cellular cytotoxicity (ADCC) (8), a mechanism that improves the oncolytic activity of mAbs.
- Tandem α-1,3 galactosylation is a non-human glycosylation motif that is produced by murine cell lines, such as NS0 and Sp2/0 (9) and has also been observed in CHO cells (10). Presence of α-1,3 galactose residues has been reported to cause fatal anaphylaxis in patients treated with Cetuximab (Erbitux, Bristol-Myers Squibb/Merck) (9,11). These cases occurred in patients who were allergic to α-galactose, a condition likely caused by exposure to tick bites (9,11). To avoid these reactions, patients are now screened for α-galactose allergy prior to treatment with Cetuximab (9,11).
  - The absence of core fucose has been reported to enhance mAb ADCC activity up to 50-fold in in-vitro studies (12). Cell engineering strategies to eliminate core fucosylation have resulted in two commercially-available glycoengineered mAb products, mogamulizumab (Poteligeo, Kyowa Kirin) and obinutuzumab (Gazyva, Roche).
  - High levels of β-1,4 galactosylation on the Fc glycans of mAbs enhance their complement-dependent cytotoxicity (CDC) (13) and ADCC (14). High β-1,4 galactosylation is, therefore, a preferable attribute of oncolytic mAbs.
  - High levels of α-2,6 sialylation have been linked with enhanced anti-inflammatory activity in intravenous immunoglobulin (IVIg) therapies (15) and would, thus, be a desirable attribute of immune-modulating TGs, such as adalimumab (Humira, AbbVie) and Enbrel. Importantly, the anti-inflammatory properties of sialylation are exclusive to the glycosidic bond conformation (α-2,6) and the sialic acid species (N-acetylmuraminic acid, Neu5Ac) involved (15). CHO, NS0, and Sp2/0 cell lines only produce α-2,3 bonds and may also produce sialylation with N-glycolyl neuraminic acid (Neu5Gc), a moiety that may be immunogenic in humans (16). Higher Neu5Ac sialylation has also been reported to increase the serum half-life of TGs (17).

PROTEIN GLYCOXYLATION IN MAMMALIAN CELLS

Protein asparagine (N)-linked glycosylation occurs in two steps (18). The first occurs while the protein is being...
For the purposes of this review, the glycosylation process is considered to have two distinct inputs. The first encompasses the enzymes, which catalyze the monosaccharide removal and addition reactions (glycoenzymes). The second input for the glycosylation processes consists of nucleotide sugar donors (NSDs), which are metabolites that provide monosaccharides for the sugar addition reactions of the glycosylation process. NSDs are endogenously synthesized by the production cell lines using common nutrients, such as glucose and glutamine, as substrates (21). Thus, NSDs are the direct link between cellular metabolism (i.e., nutrient availability) and TGP glycosylation. Many cell culture NSD precursor feeding strategies have been developed to tune TGP glycosylation (22,23).

MODELS OF THERAPEUTIC PROTEIN GLYCOSYLATION (2009 TO 2019)
The first model for N-glycosylation, published in 1996, aimed to describe the addition of glycans to the peptide backbone of proteins (24). From then, N-glycosylation models expanded to include the extent of glycan processing within the Golgi apparatus, thus aiming to depict the variability observed in TGP glycosylation profiles. Descriptions of glycosylation soon required strategies for automatically generating the complex reaction networks involved in the process and were pioneered by Krambeck and Betenbaugh in 2005 (25). Building on these seminal studies, more than 20 mathematical models for protein glycosylation have been developed to date. Based on structure and solution strategy, the mathematical models of TGP glycosylation can be grouped into three categories: kinetic models, flux-based models, and statistical models.

Kinetic models attempt to capture the time-dependent mechanisms underlying glycosylation and are based on dynamic material balances for all TGP s and NSDs present in Golgi (26–28). Given the inherently dynamic nature of cell culture processes, kinetic models are particularly suited to describe the effects bioprocess conditions have on TGP glycosylation. A fundamental drawback of kinetic models is that they require a substantial amount of experimental data to determine robust values for their unknown parameters (e.g., enzyme kinetic rate constants).

Flux-based glycosylation models consist of material balances for all TGPs present in the Golgi apparatus and are built using reaction networks that define the production and consumption stoichiometry of each species. To solve flux models, steady state is assumed, and the resulting system of linear equations is solved for the rates (fluxes) at which all TGPs are interconverted. Because the resulting system of linear equations is usually underdetermined (more unknown fluxes than equations), flux models must be solved using constraint-based linear programming (29,30) or probabilistic methods, such as Markov chain Monte Carlo simulations (31,32). A key advantage of flux-based models is that their solution requires reduced amounts of experimental data. The main drawback of flux-based models is that their solution inherently assumes steady state, which limits their ability to describe the dynamic shifts in TGP glycosylation often observed in cell culture processes. This limitation has been recently addressed by including parameters representing dynamic shifts in TGP residence time within Golgi (30).

Statistical models are abstract black-box mathematical representations where process inputs are quantitatively related, via statistical regression strategies, with TGP glycosylation profiles. Examples of statistical models of TGP glycosylation are design of experiment (DoE) surface response models (23) and partial least squares regression (33,34). Advantages of statistical models are that they do not require a priori knowledge of the process, require little or no end-user modeling expertise, and can therefore be deployed with relative ease. Statistical models are limited in that they are exclusively data-driven and, thus, are unable to yield insight into the mechanisms underlying TGP glycosylation. Furthermore, the predictive capability of statistical models may break down if model inputs drift outside the input space with which they were calibrated.
Table I. Mathematical models of protein glycosylation (2009–2019).

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Model type</th>
<th>Therapeutic glycoprotein (TGP) glycosylation quality assurance (QA) applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krambeck et al. I (35)</td>
<td>2009</td>
<td>Kinetic</td>
<td>Matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) glycan data analysis for cell line characterization.</td>
</tr>
<tr>
<td>del Val et al. (36)</td>
<td>2011</td>
<td>Kinetic</td>
<td>In-silico cell line glycoengineering.</td>
</tr>
<tr>
<td>Bennun et al. (37)</td>
<td>2013</td>
<td>Kinetic</td>
<td>MALDI-TOF glycan and transcriptomic data analysis for cell line characterization.</td>
</tr>
<tr>
<td>Grainger &amp; James (23)</td>
<td>2013</td>
<td>Statistical</td>
<td>Design of experiments (DoE) surface response model for at-line bioprocess control.</td>
</tr>
<tr>
<td>Ohadi et al. (38)</td>
<td>2013</td>
<td>Kinetic</td>
<td>Predicts dynamic variations in monoclonal antibody (mAb) glycans for bioprocess characterization.</td>
</tr>
<tr>
<td>Jedrzejewski et al. (21)</td>
<td>2014</td>
<td>Kinetic</td>
<td>Predicts dynamic variations of mAb glycans from extracellular nutrient availability for bioprocess characterization.</td>
</tr>
<tr>
<td>Hang et al. (29)</td>
<td>2015</td>
<td>Flux-based</td>
<td>Glycan data analysis for protein and cell line characterization.</td>
</tr>
<tr>
<td>del Val et al. I (26)</td>
<td>2016</td>
<td>Kinetic</td>
<td>Predicts dynamic variations of mAb glycans for bioprocess characterization, cell line selection and in-silico glycoengineering.</td>
</tr>
<tr>
<td>del Val et al. II (39)</td>
<td>2016</td>
<td>Reconstruction</td>
<td>Defines the nucleotide sugar donor (NSD) demand towards cellular glycosylation for cell line characterization and bioprocess control.</td>
</tr>
<tr>
<td>McDonald et al. (40)</td>
<td>2016</td>
<td>Reconstruction</td>
<td>Automated framework for O-glycosylation reaction network reconstruction for cell line characterization.</td>
</tr>
<tr>
<td>Spahn et al. (31)</td>
<td>2016</td>
<td>Flux-based</td>
<td>In-silico Chinese hamster ovary (CHO) cell line glycoengineering.</td>
</tr>
<tr>
<td>Villiger et al. (41)</td>
<td>2016</td>
<td>Kinetic</td>
<td>Predicts dynamic variations of mAb glycans from cell culture conditions for bioprocess characterization and control.</td>
</tr>
<tr>
<td>Hutter et al. (30)</td>
<td>2017</td>
<td>Flux-based</td>
<td>Predicts dynamic variations of mAb glycans from manganese supplementation for bioprocess characterization and control.</td>
</tr>
<tr>
<td>Karst et al. (42)</td>
<td>2017</td>
<td>Kinetic &amp; Statistical</td>
<td>Compares kinetic and statistical models for perfusion bioprocess optimization and control.</td>
</tr>
<tr>
<td>Krambeck et al. II (27)</td>
<td>2017</td>
<td>Kinetic</td>
<td>MALDI-TOF glycan and transcriptomic data analysis for cell line characterization and in-silico cell line glycoengineering.</td>
</tr>
<tr>
<td>Sokolov et al. I (43)</td>
<td>2017</td>
<td>Statistical</td>
<td>Used to design cell culture media to achieve glycosylation biosimilarity of a mAb (bioprocess optimization and control).</td>
</tr>
<tr>
<td>Sokolov et al. II (34)</td>
<td>2017</td>
<td>Statistical</td>
<td>Predicts dynamic variations of mAb glycans from cell culture conditions for bioprocess characterization and control.</td>
</tr>
<tr>
<td>Sou et al. (44)</td>
<td>2017</td>
<td>Kinetic</td>
<td>Predicts dynamic variations of mAb glycans from cell culture conditions for bioprocess characterization and control.</td>
</tr>
<tr>
<td>Spahn et al. (32)</td>
<td>2017</td>
<td>Flux-based</td>
<td>In-silico CHO cell line glycoengineering for glycosylation biosimilarity.</td>
</tr>
<tr>
<td>Aghamohseni et al. (45)</td>
<td>2017</td>
<td>Kinetic+flux-based</td>
<td>Predicts galactosylation from cell culture conditions for bioprocess characterization and control.</td>
</tr>
<tr>
<td>Kremkow &amp; Lee (46)</td>
<td>2018</td>
<td>Flux-based</td>
<td>In-silico CHO cell line glycoengineering.</td>
</tr>
<tr>
<td>Sokolov et al. III (33)</td>
<td>2018</td>
<td>Statistical</td>
<td>Predicts dynamic variations of mAb glycans from cell culture conditions for bioprocess characterization and control.</td>
</tr>
<tr>
<td>Kotidis et al. (47)</td>
<td>2019</td>
<td>Kinetic</td>
<td>Used to design an optimal NSD precursor feeding strategy that maximizes mAb galactosylation while maintaining product titer.</td>
</tr>
<tr>
<td>Le et al. (48)</td>
<td>2019</td>
<td>Reconstruction</td>
<td>Automated framework for O-glycosylation reaction network reconstruction/visualization for cell line characterization.</td>
</tr>
</tbody>
</table>

Table I presents the glycosylation models that have been developed since 2009 and highlights how each model has been used toward potential TGP quality assurance applications.

DEPLOYMENT OF GLYCOSYLATION MODELS FOR BIOPHARMACEUTICAL QA

Table I shows that all published glycosylation models have been used for applications that can directly support TGP QA practices. Four QA application areas stand out: (i) data analytics, (ii) bioprocess characterization, (iii) cell line engineering/development, and...
(iv) manufacturing bioprocess optimization and control.

Kinetic models appear to be the most versatile, having been used for all four application areas. Flux-based models have mainly focused on cell line selection and glycoengineering, and statistical models have been used for bioprocess characterization, control, and optimization. The application areas for the different modeling strategies result from their underlying features. Because kinetic models aim to mechanistically describe the glycosylation process, they are capable of covering all QA application areas. Flux models are well-suited to define cell glycoengineering strategies because they focus on the rates of glycoenzyme-catalyzed reactions. By definition, statistical models quantitatively represent correlations between bioprocess conditions and TGP glycosylation. Therefore, they are particularly adept for bioprocess control and optimization QA applications when mechanistic bioprocess knowledge is lacking.

Although the deployment of statistical models in industry is increasing at an accelerated pace (49), the use of mechanistic glycosylation models remains to be widespread. This disparity may arise from the use of specialized software and the perceived need for expert user input associated with mechanistic modeling. Despite these challenges, mechanistic models are, conceptually, more versatile than their statistical counterparts because they are based on the biochemical mechanisms underlying the glycosylation process. An interesting example where these limitations are addressed is the GLYMMER (ReaTech) software platform, which is based on the work by Bennun et al. (37), runs on Microsoft Excel, and requires only moderate user input and expertise.

CONCLUSION

The deployment of different glycosylation modeling strategies depends entirely on the TGP quality assurance application they will be used for. Statistical models can be readily deployed in the industrial setting for bioprocess design, control, and optimization (33,43) with minimal user input and expertise. Mechanistic models (kinetic and flux-based) have been shown to be particularly robust for cell line characterization (27,50) and glycoengineering (26,31) as well as for bioprocess design and optimization (42,47).

To fully exploit the advances in glycosylation modeling toward the development, control, and optimization of next-generation TGP production bioprocesses, close collaboration between academic and industrial groups must continue so that the models are fit for purpose and require minimal end-user expertise for deployment.

REFERENCES

Going Global in Biopharma Regulatory Affairs

Globally accepted products are becoming increasingly in demand, leading to more need for regulatory harmonization, particularly for biosimilars.

FELICITY THOMAS

The biopharmaceutical regulatory landscape is continually shifting and adapting, mirroring the innovative nature of the industry and ultimately ensuring the safety of all stakeholders. With increasing demands for globally accepted solutions to mitigate the rising development costs, further regulatory harmonization would undoubtedly be beneficial to patients and manufacturers.

Currently, however, there remain some key differences between national regulatory requirements within the biopharmaceutical space. “Arguably, the most significant difference between national/regional regulatory bodies is in the way that follow-on biologics are developed and assessed,” says David Deere, chief commercialization officer for PaizaBio.

REGULATORY VARIANCES

There is generally a good level of understanding about medicines evaluations within the classic innovator countries/regions (such as the United States and Europe). Within the US, any biological product is submitted for assessment to FDA, and in Europe, human medicines derived from biotechnological processes are evaluated by the European Medicines Agency (EMA).

“In Australia, biologicals refer only to human cells and tissues,” confirms Alexandra Isabel Rosa, regulatory affairs associate at ELS Solutions. “Hence, vaccines (that do not contain viable human cells), recombinant products, and blood-derived products are not considered biologics and are treated by the national authority (the Therapeutic Goods Administration) as medicines or medical devices.”

Registration of new biological entities in South Africa usually occurs following the registration by at least one international regulatory authority the South African regulatory authority is aligned with, usually EMA or FDA, Rosa continues.

“In Switzerland and New Zealand, the biological application may happen after approval in a reference jurisdiction (such as Europe) or in parallel with the European Union and US submissions,” she adds. “This approach generates a reduction of submission fees.”

There is an understandable recognition by the regulatory bodies, however, that biologics require a different knowledge and skillset than traditional pharmaceuticals (small molecules), emphasizes Deere. “This presents a problem of obtaining trained staff among domestic experts in many markets,” he adds.
In China, which has vast market potential, particularly compared with other emerging markets, there is an expansion of regulatory review staff within the National Medical Products Administration (NMPA, formerly CFDA) underway. “The staff levels have been expanded by five times since 2015, and the NMPA has plans to double the number of staff again by 2020,” Deere notes. “Through a variety of avenues including the Gates Foundation, the NMPA has secured access to highly experienced professionals from FDA/EMA that have helped train their new staff as they ramp-up oversight of the burgeoning Chinese biomanufacturing sector.”

**BIOSIMILAR CONSIDERATIONS**

Biosimilar products are biologicals that have similar structure, biological activity, efficacy, safety, and immunogenicity to an approved biological medicine, which is referred to as the innovator or reference medicine. “However,” Rosa adds, “Biosimilar products are not considered generics of biological products because of the manufacturing process, which is complex and implies some intrinsic variability.”

According to Patricia Hurley, senior director, PPD Consulting, it should be noted that several biologics (in particular some interesting monoclonal antibody products) are coming ‘off patent,’ which will undoubtedly lead to an upswing in biosimilar development. “For biosimilar medicinal products, the ‘regulatory bar’ remains at a higher level, with regulators expecting to see a stepwise approach throughout the development program,” she adds.

John Watkins, associate director, regulatory affairs, PPD, concurs. “This high regulatory requirement is a result of the natural variability and more complicated manufacturing process for biopharmaceuticals by cell culture in a bioreactor, which preclude an exact replication of microheterogeneity (1). Therefore, more studies are required for regulatory authority approval of biosimilars than for a generic version of small molecule products.”

When addressing the regulatory body required information, the dossier for a biosimilar will not only differ from that of the reference medicine but may also vary depending upon the approving region/country. “While both EMA and FDA require similar clinical development standards from sponsor companies including full pharmacokinetic/pharmacodynamic bioequivalence comparisons to the innovator/reference biologic as well as limited phased clinical development to establish comparative safety and efficacy, EMA does not address the issue of ‘interchangeability,’ which is predominately a US legislative artefact,” Deere reveals.

“Biosimilar designations for both FDA and EMA require that the biosimilar demonstrates no ‘clinically meaningful differences’ between the sponsored biosimilar being evaluated when compared with the reference innovator biologic,” he adds. “But, FDA has an ‘additional’ category for interchangeability, which requires additional clinical trials that evaluate ‘switching’ patients from branded reference to the biosimilar instead of the standard naïve head-to-head comparisons.”

The expectations of FDA and EMA are clear in terms of biosimilar development, and are laid out in the relevant guidance documents, Watkins stresses. “Several countries have adopted the overarching principles of these ICH jurisdictions, such as Australia, India, and Saudi Arabia, to name but a few,” Hurley adds. “Biosimilar developers should be aware that even though EMA and FDA biosimilar guidelines refer to the ‘totality of evidence’ regarding the quality, nonclinical, and clinical data packages, EMA and FDA will require the applicant to demonstrate similarity with the reference medicinal product at the quality level (1). Having very comprehensive and robust clinical and nonclinical data packages will not compensate for having a limited quality data package.”

For Deere, regulatory requirement variances can be more pronounced in emerging countries, where many follow-on biologics are simple biological ‘copies’ of an innovator product. “These ‘biogenerics’ are standard in India and predominate in China,” he adds. “While a biological copy may have similar characterization and varying standards of established bioavailability, they do not have established comparable safety and efficacy based on comparative clinical trials.” Although, Deere notes that China’s NMPA has now adopted a biosimilar approval pathway that features similar requirements to those of the US and Europe, with the country’s regulatory body approving its first biosimilar in February 2019 (2).

Even within the European Union, there are differences, particularly relating to the issue of interchangeability. “EU member states treat the issue of interchangeability differently, with some countries allowing biosimilars carte blanche formlulary interchangeability while others leave it up to subscribing physician discretion,” Deere adds. “As a result, this ‘issue’ has been exploited by innovator companies in defense of branded products, sowing doubt within the medical community, which has negatively impacted adoption of cost-saving biosimilars; especially in the US. Studies are confirming interchangeability of approved biosimilars (3) leading to rapid adoption of biosimilars over branded biologics because of cost savings.”

However, Deere specifies that to date, while there have been 18 biosimilars approved by FDA, only seven are on the market. “Three are recent approvals, the rest face a thicket of process patent litigations and have been voluntarily delayed in exchange for a licensing grant to market the drug in other regions, namely the EU, by the innovator company,” he says. “The remaining companies are involved in on-going litigation and have chosen to delay their biosimilar launch. None of the biosimilars in the US have been approved as interchangeable.”

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HARMONIZATION EFFORTS
Regulatory harmonization ensures that common compliance standards are met and sustained, ultimately protecting the consumer’s safety and health, explains Rosa. “Relevantly, harmonization also facilitates market access, making new drugs available for patients that otherwise would not have therapeutic alternatives,” she says.

Through a synchronized system, regulatory bodies could also benefit as duplicated inspections are avoided, which allows for greater focus on sites that could have a higher risk and could broaden the inspection coverage of the global supply chain, Rosa continues. Additionally, for manufacturers, the reduction in the number of inspections that they will be subjected to implies that there will be a reduction in cost.

“Harmonization efforts have mainly assumed the form of mutual recognition agreements (MRAs), which require regulatory agencies to recognize each other’s competence and equivalence,” says Rosa. “For example, FDA and EMA entered into one such MRA in November 2017, although this is transitional and is not expected to be completed until July 2019 (4). The EU has other MRAs in place with Australia, Canada, Israel, Japan, New Zealand, and Switzerland.”

An important aspect of the MRAs for Deere is that they relate to ‘foreign’ manufacturing inspections, which he notes is particularly prudent for emerging countries, such as China and India, as through these agreements there will be better exchange of reports. “Of course, the International Council for Harmonization (ICH) is also constantly attempting to harmonize regulations,” he adds. “China’s membership in June 2017 and subsequent Management Committee ship in June 2018, further, serves to ‘obligate’ China to ICH global standards.”

A GLOBAL APPROACH TO REGULATORY AFFAIRS
A frequent approach taken by most developers is to file for marketing authori-

zation in Europe or the US prior to targeting other markets. “The reason for this approach is that applicants may take advantage of the scientific advice and pre-submission meetings provided by these authorities on quality, non-clinical, and clinical aspects of applications, which will allow the development of more complete dossiers, that meet regulations and expectations, and contribute to the decrease of time for revision and approval,” notes Rosa. “It is not essential to ask for scientific advice with authorities of other markets as advice received from FDA or EMA will typically cover global requirements.”

In Deere’s opinion, the product type will have an important part to play in the marketing approach. “For truly innovative, first-in-class products which offer substantial therapeutic value, the higher price-points of the developed markets (US/EU, Japan) will likely remain the targeted launch markets, with China also included, assuming there are no major risks to the molecule,” he says. “For biosimilars and novel but non-first-in-class products, regional strategies might be appropriate dependent upon market environment. Of course, national or regional disease population demographics might warrant local/regional therapeutic need, such as malaria and other infectious diseases.”

When looking at regulatory affairs, however, Deere states there is a simple correlation that if a company is global then its approach to regulatory affairs should be global. “In addition to uniform product safety monitoring, all development teams and product teams should have international regulatory affairs as a component,” he says. “What is ultimately going to happen is that, with minimal exception, corporate development portfolios will be developed by global project teams, simultaneous in the three regions: US, EU, and China.”

Rosa highlights the need for regulatory affairs departments to perform regular literature searches to keep pace with regional, local, and global regulation changes. “Global companies should have locally specialized regulatory teams, whose qualified members should be allowed to circulate within global departments to give and receive training, mitigating both regulatory risks and costs,” she adds.

OUTSOURCING: A VIABLE ALTERNATIVE?
Alternatively, companies can outsource regulatory services. “Smaller contract research organizations and specialist regulatory consultancies certainly can offer most regulatory services, while the larger providers can offer them on a full global basis,” explains Alistair Davidson, executive director, regulatory affairs, PPD. “With the evolution of the global regulatory landscape and pressure on pharma companies to control costs, many companies are looking for effective outsourcing to ease costs while continuing to deliver quality outputs.”

Davidson continues to explain that for companies that have medium-to-large global product portfolios the majority of regulatory work occurs in the post-approval phase—mainly relating to the maintenance of marketing authorizations. “Such activities lend themselves well to outsourcing as a lot of them are predictable and relatively routine, although they do have key time- and quality-related compliance criteria,” he says. “A significant proportion of such work, including work traditionally done by local regulatory teams at the company/country/affiliate level, can be delivered from dedicated remote or virtual centers conferring greater consistency, efficiency, and effectiveness.”

Although Deere agrees that mid-sized companies seeking geographic expansion, particularly into emerging markets, can benefit from outsourcing regulatory processes for filing purposes, he cautions that once a product is on the market in-house responsibilities are key. “Once a product reaches market, safety and continued compliance, as well as future products should be ‘in-house’
and directly reportable to global regulatory affairs,” he states. “Scientists, clinicians, and certainly commercial teams too often forget that the first ‘customer’ for their product is regulatory agencies, which do not like being ‘ignored’ before/during new drug application/marketing authorization review/approval, or afterwards. ‘Relationships’ cannot be outsourced, and as any lawyer or regulatory affairs professional will advise, corporate liability is inherent in the product sold regardless of geography.”

WHAT THE FUTURE HOLDS

There is a current wave of digital solutions impacting the bio/pharma industry. For Rosa, artificial intelligence (AI) is of particular note as it is influencing drug discovery as well as disease diagnosis and monitoring. “However, in my opinion, AI will also enable the management of regulatory challenges that manufacturers presently face,” she says.

Rosa explains that the advantage of AI-powered customer relationship management (CRM) software in addressing and solving innovation and pipeline problems is twofold. “Firstly, this software will provide the desired product for the health platform sought, pre-qualified in terms of regulatory status, lead time, and supply price pre-negotiated to fall in target-net present value bandwidth,” she adds. “Secondly, these systems will map out processes that entail the innovation effort from all relevant departments in tangible and pre-negotiated workflow and service-level agreements.”

“To me, the most pressing technical issue is what role continuous manufacturing will play,” emphasizes Deere. “If the logarithmic increase in yield over large-scale bioreactors can be successfully scaled, a lot of manufacturing space/capacity could be made redundant, very quickly! And, of course, downstream purification offers lots of opportunity for improvement, which represents huge regulatory challenges.”

Technical advances may also usher in significant cost savings, particularly considering biosimilars, notes Deere. “These cost implications could be proportionally similar to those witnessed in the small-molecule generic field 30 years ago,” he adds.

Additionally, the ability of developers to demonstrate comparable safety and efficacy of biosimilars with the innovator product will become the industry standard, Deere continues. “The rubric of interchangeability will drop from the vocabulary as sponsor companies include switching arms in clinical efficacy trials and data confirm that biosimilars equal interchangeability in all patients both in safety and efficacy,” he summarizes. “As the ‘comfort-level’ rises among regulators that large biologics can be successfully manufactured via standardized biomanufacturing procedures and that these ‘copies’ truly translate as clinically comparable to the innovator/reference product in patients, clinical development requirements for biosimilars will likely be reduced accordingly.”

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Where Automation Meets Skill Set
This article takes a look at the skill sets and training needed to tackle the increasing levels of automation in bioprocessing facilities.

FELIZA MIRASOL

The need for skilled bioprocessing professionals remains a major concern in the biopharmaceutical industry, even as automation plays an increasing role on the manufacturing floor. Although the role of automated systems in bioprocessing is to reduce human interaction, and therefore the risk of contamination or user errors, in the manufacturing cycle, a certain level of operator oversight is still required.

This need is coupled with the pressure the biopharmaceutical industry is facing as the older generation of bioproduction staff begins to retire, amid a rapid increase of biomanufacturing facilities coming online. In addition, newer manufacturing technologies for gene therapies and cell therapies are added to the mix as these therapeutic products ramp up in the commercial space (1).

TRADITIONAL TRAINING

Important to keep in mind is that training needs can be highly variable from company to company, thus making a one-size-fits-all approach impractical. It is therefore recommended that all aspects of training—including design, development, and delivery—be customized to meet specific company needs (2). Because of the variety in practices and technologies, however, training cannot be readily standardized, which is a concern for biomanufacturing companies. The industry would have to be adaptive to customized training, which has been a significant obstacle in the current biomanufacturing climate where the overall attitude is conservative to changes (3).

Biopharmaceutical industry consultants recommend that training programs be accredited by a nationally recognized educational body to ensure high-quality standards and effectiveness of the training, but there is a general lack of interest in the industry for such formalized training. Instead, companies have been content to rely on existing courses that comply with certain standards. The lack of accreditation or certification, however, is especially an issue for advanced-level, specialized training (2, 3).

There is a general belief that, since the industry has never been credentialed, to do so now would pose a challenge, especially concerning the transferability of skills and competencies. Biotech facilities typically differ in equipment, pro-
Analysis of subvisible and visible particles—including foreign particles, protein aggregates from the API in biologics, microbubbles, and silicon oil droplets—is required as part of lot release. Recent years have seen advances in analysis technology, as well as studies to understand and assess biological consequences of these particles. Characterization of aggregates/particles should be part of product characterization during development, resulting in an understanding of what is normal for a product.

This webcast will explore the analytical methods available for particles/aggregates ranging in size from submicron to visible particles, with emphasis on the subvisible particles (1–100 μm).

Topics for discussion include:

- A brief overview of the historical safety concerns
- The current state of analysis across the industry
- A discussion of a phase-appropriate, risk-based approach

**KEY LEARNING OBJECTIVES**

- Understand historical origins of classifications of subvisible and visible particles
- Awareness of analytical techniques available, and phase appropriate applications
- Awareness of available references including compendial chapters

**WHO SHOULD ATTEND:**

- Lab managers, principal scientists, R&D, analytical, QA/QC scientists at biopharmaceutical companies
- Scientists at CDMO’s and contract analytical labs
- Regulatory experts working in the field of biologics

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For questions contact Kristen Moore at kmoore@mmhgroup.com
cesses, and other factors, which would still require someone with knowledge to receive on-site training to reach competence (3).

Yet, the bioprocessing industry continues to invest in training, which it sees as a major requirement for avoiding problems and capacity constraints. New practices, such as online components, use of customized training, and the development of accredited/certified training have not yet been adopted, but new methods may be needed as bioprocessing grows globally and the added nuance of automation implementation is increasingly adopted.

QUALIFIED RECRUITS
In an interview with BioPharm International, Loe Cameron, director of Analytics & Controls at Pall Corporation, offered some insights into the need for developing a sufficiently trained bioprocessing workforce capable of operating in an increasingly automated world.

BioPharm: How do manufacturers find sufficient qualified personnel?

Cameron: This is a challenge as the required skills are evolving with the technologies, and demand has increased for highly skilled workers versus technicians and operators. If we look at recruitment trends, the industry has long been preparing for a gap in qualified personnel as the market expands beyond the number of newly available candidates and competition increases for existing talent. Because of this, we think it is important to not just focus on recruiting new talent, but also on retaining the existing workforce and making them part of the future. A strategy of both recruitment to supplement teams with new skill sets and continuing education (training) of existing personnel to stay relevant provides the best chance at business continuity and sustainable growth.

To bring in new recruits, it is becoming increasingly necessary to search outside both our industry and manufacturing as a whole, which creates challenges and opportunities. Automation talent from other industries, which are less closely regulated, may have experience with new approaches with great benefits to bioprocessing; however, they will need training in how to apply that knowledge in our regulated environment. Additionally, the drive to Pharma 4.0 and greater network security introduces implementation challenges more familiar to information technology (IT) professionals than the operational technology (OT) professionals who manage manufacturing today. This IT/OT convergence opens up a much larger skilled workforce to our recruiting efforts but could create risks if teams aren’t able to build a collaborative environment around their various strengths and weaknesses.

Biotech facilities typically differ in equipment, processes, and other factors, which would still require someone with knowledge to receive on-site training to reach competence.

Retention of existing resources and the associated tacit knowledge, reaching into other industries to broaden the talent pool, and building consensus between IT/OT are all needed to ensure we have the right teams to take us into the future.

BioPharm: How do employee skill sets fit into the design and operation of new equipment and systems? Or, vice versa?

Cameron: In the manufacturing suite, we are starting to see a philosophical shift from training the employee to operate the equipment to designing the equipment around the employee. Greater importance is being placed on the human factors of equipment and system design, and vendors are taking more time to evaluate and research how the equipment and systems are used, and what that user experience is like.

Approaches such as usability trials and human machine interface (HMI) optimization provide value by reducing risk across the entire lifecycle of the equipment. This approach lowers skill and training requirements on the manufacturing floor but requires new skills in equipment design. Industrial designers, user experience specialists, and ergonomics engineers are getting more involved in the development of manufacturing equipment and making significant changes in how these products are realized.

FUTURE FACILITIES
BioPharm: What levels of automation should be expected in bioprocessing facilities in the future?

Cameron: The level of automation should be based on business goals, with a focus on making progress and de-risking wherever possible. We see automation as a tool rather than a goal. Since the advent of automation, there has been a drive to automate as many actions as possible to lower cost and risk while increasing quality, but there is also risk in automating too quickly.

In our industry, the best approach is to apply major technology changes incrementally so that we can understand the impact on the process and product. We also pay close attention to what other industries have experienced as we look to mitigate risks.

Overall, this industry has a very low tolerance for risk, so companies must
ensure that automation efforts reflect that and gather as much insight as possible. Gathering information can also be part of the automation solution through process modeling and the eventual creation of processes that are self-optimizing. As a deeper understanding of the process is gained, we can make better use of data and apply automation where it will have the greatest impact.

“In our industry, the best approach is to apply major technology changes incrementally so that we can understand the impact on the process and product.”
—Loe Cameron, Pall Corporation

**BioPharm:** Looking to the future, what impact will automated bioprocessing facilities have on the way staff are hired and the quality of staff that will be required?

**Cameron:** Humans still have to be involved in the process, no matter how far automation is implemented. At Pall, we are not looking to remove personnel, but rather provide positions that are more satisfying and offer a greater trajectory through automation. We want to minimize mindless work and allow our personnel the freedom to pursue continued education and grow with our team. It is no secret that turnover is a huge problem for this industry, so we feel that by providing more engaging and meaningful work, we can all grow together.

**INVESTMENT AND SYSTEM KNOW-HOW**

**BioPharm:** How much time and investment are typically needed to train personnel in automation systems, especially with newer systems and/or integrated systems?

**Cameron:** This depends on the level of automation. With thoughtful automation, training requirements can potentially be lowered by building standard operating procedures and sequences into the systems themselves. The manufacturing personnel and automation become a team when the control systems continuously reinforce taking the next step, the right way. For redundant or repetitive functions that can be fully dedicated to the control system, automation removes not only the training requirement but the risk of mistakes and a less engaged workforce.

Ultimately, we find that by investing in the right automation and personnel, employees come up to speed rather quickly, which helps to streamline investment.

**BioPharm:** Are there sufficient monitoring, control, and data collection technologies available? Is the know-how to use these available?

**Cameron:** Lack of automation technologies is not a major concern, but technology selection and applications are very important. Planning and projecting is critical. Long-term automation goals should be considered upfront so technology selections can be made in a way that does not cause delay or increase costs. Licensing models in the space are incredibly complicated and often have long-term impacts on operating expenses, and foundational systems like historians or automation platforms can have impacts on the implementation of future capabilities. Early development of a roadmap is critical.

While there isn’t a lack of technologies, we are often not the core market for the vendors that supply them. As a result, we often have to educate and take a bigger role in deployment than we would if we were in other industries. The specifics for data integrity must be considered and openly discussed from the start, which ultimately helps vendors to better adapt to what our industry requires.

“The manufacturing personnel and automation become a team when the control systems continuously reinforce taking the next step.”
—Loe Cameron, Pall Corporation

And because know-how can be limited and installation requires investment, we are seeing the vendors (Pall included) making larger investments in simplifying solutions for customers so that they are more cost-effective, reliable, and faster to implement.

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Predictability Improves Prospects for Biopharma Patent Holders
While it may not be getting easier, biopharma patent protection is at least becoming more predictable.

AGNES SHANLEY

Protecting biopharmaceutical patents has always been challenging, especially in the United States, birthplace of the biotech industry. In 2018, the US ranked 12th out of 50 nations in the world based on how effectively it protected its homegrown innovation, according to the US Chamber of Commerce’s annual Intellectual Property (IP) Index (1). It had ranked 10th out of 50 the previous year. In 2018, Andrei Iancu, then newly appointed director of the United States Patent and Trademark Office (USPTO), acknowledged the need for policies that would support innovators and increase the reliability of patents (2).

Overall, IP protection difficulties intensified in 2012 when the America Invents Act established the practice of using inter-partes review (IPR) to question patent validity (3,4). In 2018, the US Supreme Court upheld the constitutionality of IPRs (5). For biopharma patent holders, this decision means that the path going forward will be “a lot more certain than it had been,” says Kevin Noonan, Partner at McDonnell Boehnen Hulbert & Berghoff LLP and chair of the firm’s Biotechnology & Pharmaceuticals Practice Group.

Enhanced certainty around IPRs helped drive the US up from 12th to second place in the US Chamber of Commerce’s 2019 IP Index, according to Patrick Kilbride, senior vice-president of the Chamber’s Global Innovation Policy Center (6). For biopharmaceutical companies, which spend more on R&D than companies in any other industry in the US, patenting the companion diagnostics used in personalized medicine is extremely difficult, as was shown by the Sequenom case in 2015 (7). Kevin Noonan touched on changes and the new IP legal climate in an interview with BioPharm International.

IPR PATENT INVALIDATION
BioPharm: What impact did IPRs have?
Noonan: The bad patents were challenged first, and the invalidation rate for all industries was initially around 80–90%, but that number has since come down. The patent invalidation rate was never that high for biopharma, but it was still around 60%.

BioPharm: A few years ago, Allergan had transferred sovereign rights to its patent to a Native American tribe, to
protect it against invalidation by the IPR. Since then, we’ve heard that the US Supreme Court will be asked to rule on agreements of this type. Will this type of defense continue in the future?

Noonan: It was a very clever attempt, but the approach, ultimately, has not panned out. The Supreme Court may intervene because its justices have tended to take the position that narrowing or expanding tribal immunity is within the province of Congress, so Congress can pass a law saying that sovereign immunity won’t apply in these cases. Two years ago, lawmakers introduced bills in Congress to do just that.

STRATEGIES FOR ANTIBODIES

BioPharm: You have talked about IP protection strategies for antibodies, and use of the ‘written description’ concept. What is happening in this area?

Noonan: From 1996 to 2009, the concept was very controversial. It is based on the idea that, if you don’t describe an invention sufficiently, even if you have enabled someone else to make that invention, you aren’t entitled to a patent. This came up in the Ariad case (8). Last year, Chief Judge Prost changed the law and the way it was being applied to antibodies (9). The law now reads in a way that is consistent with the rest of the written description law that was sanctioned under Ariad. Basically, it says that the amount of description you have to do narrows the scope of the claims that you can get for antibodies in a way that would make it easier for a competitor to come on the market. This will make it more difficult for a patent holder to prevent a competitor from coming on the market. We’ll have to see whether that inhibits innovation in the space.

BioPharm: What is happening with diagnostics patents?

Noonan: Director Iancu is continuing efforts to make sense of, and better harmonize, the way that the patent office is examining applications for subject matter eligibility under 35 U.S.C. § 101, and to try to do that in a way that is consistent with Supreme Court and other decisions.

Diagnostics claims are very important and they are part of personalized medicine. A lot of the IP surrounding that effort is falling afoul of the way that the patent office, district courts, and Federal Circuit have interpreted Supreme Court teachings on this matter. Two positive developments have been the Berkheimer Tech (11) and Vanda (12) cases. In Berkheimer, the court said that sometimes the question of whether or not something is patent eligible contains the question of fact. This is important because what often happens is that the infringer files a petition to dismiss a case, based on patent eligibility theory. The only way that they can get away with that approach is if the court decides that the decision is purely a question of law. In that case, there is no need to construe the claims and the court can do that itself. If you can convince the court that there is a disputed question of fact, it can get the patentee over the hump and into discovery, offering the innovator a chance to present information and evidence that will help the court make its decision.

In Vanda, the court ruled that method of treatment claims are patent eligible, almost per se, and that the issues that the Supreme Court was concerned about do not apply to a method of treatment. Vanda and Berkheimer are two rays of hope, after eight or nine years of negative press and negative outcomes.

US IP protection rankings fell in 2018 because of stories like Sequenom’s. The company had developed a blood test that would obviate the need for amniocentesis, and the court ruled it was not patent eligible. The company had put its blood, sweat, and tears into developing the test. The environment in the US is still not innovation friendly, and the result has been a chill on innovation, especially in personalized medicine.

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April 2019
Lyophilization — Contin. from page 35

over the past three decades, particularly in terms of impact of formulation and process on product quality, and active research in the field would further enhance our understanding of the lyophilized drug product,” summarizes Patel.

“However, our progress in the field of lyophilization demands a change in mindset,” he states. “Lyophilization is an established process to deliver a sterile product with existing infrastructure.”

There are several innovations in lyophilization already under development, notes Topp. “These include continuous lyophilization, which could increase the efficiency and throughput of the process; wireless sensors, which would allow for better control of the process and support continuous processing with closed-loop control; computational monitoring, which would allow for better design of lyophilization equipment and facilitate scale-up; and analytical methods, which are enabling more rapid development of lyophilized products and can support manufacturing by evaluating the effects of process deviations on the product,” she asserts.

“With these advancements, as well as those in PAT tools, lyophilization can be monitored and controlled to minimize processing time and cost,” adds Patel. “But, more importantly, lyophilization can deliver a quality product that is stable for commercialization.”

Ask the Expert — Contin. from page 54

be assessed and addressed in a timely manner, because these types of complaints often have regulatory reporting timelines associated with them.

Medical complaints can range from mild (e.g., headache, rash, tiredness, etc.) to serious reactions (e.g., hospitalization, suicidal thoughts, death, etc.). The more serious the medical complaint, the more aggressive the company needs to be in pursuing the investigation into the complaint. The regulatory reporting requirements for medical complaints should be specified in the SOP.

Non-medical complaints do not need to be reported to the regulatory authorities, but they should be documented and investigated. These types of complaints (e.g., smashed bottle, smashed carton, incorrect tablet count, etc.) do not need to be reported to regulatory agencies, but they still need to be investigated as they could indicate deficiencies in the manufacturing and packaging operations. There are other considerations to consider when establishing a complaint handling function, such as whether or not the company wants to try and have the product returned for examination and how the product will be handled if it is procured. Keep in mind, however, that all complaints are available for regulatory review during an inspection.

Establishing a robust and well-documented complaint handling process is a significant and an important element of a strong quality system. Thought and consideration on how complaints will be communicated to the rest of the organization and how complaint resolutions will be investigated, documented, and reported are critical elements to having a complaint function that serves the organization, the customers, and the regulatory authorities.

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A robust customer complaint handling system is an integral part of a quality management system, says Susan Schniepp, executive vice-president of post-approval pharma and distinguished fellow, Regulatory Compliance Associates.

Q: I am a quality assurance professional working for a small start-up company. I am setting up their quality management system, but I have little experience with complaint handling. Can you provide some basic advice on setting up a system to handle customer complaints?

A: A complaint handling system is a critical quality function that needs to be designed in conjunction with your quality management system (QMS). The requirements for complaint handling are well documented in the regulations (1–3). The importance of the complaint system and its relationship to other functions is often underappreciated by companies when setting up a QMS. The complaint system should be one of the first systems to be established by a company because the information gleaned from complaints feeds directly into the deviations, investigations, and corrective actions and preventive actions (CAPA) functions. Whether your product is a prescription drug (small or large molecule), over-the-counter medication, medical device, or combination product, the process for addressing complaints falls under regulatory scrutiny (4).

The first element of a robust complaint system is to establish a standard operating procedure (SOP) for complaint handling. The SOP should indicate the communication vehicle used to collect customer complaint information. These communication avenues can include, but are not limited to, use of a dedicated telephone number and/or an Internet link where customers can report the problem they are having with your product.

It may seem archaic to recommend a phone number, but it is necessary because not everyone taking your medication is comfortable with or has access to the Internet, and these individuals may be more at ease leaving a message on an answering machine. Needless to say, this is an element of the complaint handling system that might be outsourced. If you decide to outsource this activity, you should specify this in your SOP and have a quality agreement with the company that is performing this service for you.

Once the basic communication elements are determined and established, they need to be monitored on a routine frequency. The monitoring frequency should be established in the SOP for the handling of complaints. The phone line and the weblink should be monitored at a minimum once a day. It would be ideal if the communication lines could be continuously monitored, but this may be impractical for a small company. If this activity has been outsourced, the information collected on a daily basis by the service provider should be collected and reviewed on a daily basis by the company.

The next element needed for effective complaint handling is determining the information that you need from the customer. At a minimum you will want to know (4):

- Name and contact information
- Age and sex
- The name of the product
- The dosage strength, if applicable
- The name of the store where the purchase was made
- A detailed description of the problem/issue associated with the product.

Again, if you are outsourcing this function, you will need to make sure this information is being collected by your service provider.

Once you have established the communication avenues and the information requirements, you need to determine the complaint categories. There are several complaint categories that a customer might want to report to a company including medical conditions, product quality problems, preventable mistakes, and therapeutic failures. Any type of medical complaint is serious and needs to...
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