SPARKING ALTERNATIVE IDEAS FOR DOSAGE FORMS

UPSTREAM PROCESSING
THE EXPANDING LANDSCAPE OF COMMERCIAL SINGLE-USE BIOREACTORS

OPERATIONS
TEST METHODS AND QUALITY CONTROL FOR PREFILLED SYRINGES

DOWNSTREAM PROCESSING
MEMBRANE TECHNOLOGY FOR ENHANCING SEPARATION AND PURIFICATION

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

Reference Standards are associated with validated qPCR methods

<table>
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<th>Now available</th>
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<tr>
<td>• CHO Genomic DNA RS (catalog #1130710)</td>
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<td>• E. coli Genomic DNA RS (catalog #1231557)</td>
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For Reference Standards that you can trust, visit: Biologics.usp.org/BP1
Caught in a Conundrum

In late February 2019, the Senate Finance Committee called CEOs of major bio/pharmaceutical companies to Washington, DC to testify about the cost of prescription drugs. Senators bemoaned the cost burden on patients and the bio/pharma executives played up the expense of developing new drugs and a complicated payment system. For all the spectacle, expectations for real change are only slightly higher than in the past. Potential solutions under discussion include allowing Medicare to negotiate drug prices; controlling prices based on what is charged in other countries; allowing patients to import drugs from Canada; and eliminating pay-for-delay strategies that discourage generic-drug competition.

Another solution is to bring more generic drugs to market. The basic economic premise that increased competition will lead to lower product costs, however, does not always prove true for the pharma industry. Lower drug prices mean lower margins; convincing manufacturers to produce low-margin drug products—while maintaining quality standards—is not easy. Recently, prices for some generic drugs in short supply have been hiked significantly because the generic-drug manufacturer knew they had no competition.

In response to high drug prices and shortages, a consortium of hospitals launched their own drug manufacturing company; legislation called for the federal government to manufacture generic drugs if the market cannot—or will not—provide drugs at affordable prices (1); and FDA announced a Competitive Generic Therapies pathway to encourage development of generic versions of branded drugs that are off patent but have no generic alternatives (2).

Despite 15 approved biosimilar drugs and 60 in development, adoption of lower-cost biosimilars has been delayed, often due to legal tactics of innovator companies. In a December 2018 statement, FDA promised, “We’re not going to be partners to these deceptions,” and issued guidance documents designed to promote competition for biologic drugs, such as insulin (3).

Perhaps the greatest consequence of cheaper generic drugs is that lower quality products may be entering the supply chain. Recent news reports (4–7) have detailed quality issues associated with generic-drug manufacturing in the United States and abroad, questioned how the drug industry conducts inspections, and highlighted self-policing efforts by manufacturers. FDA responded with a rigorous defense of its oversight activity and the safety of generic drug products (8).

Despite the debate, patients are left to consider if they are paying a price in questionable safety and quality when they demand affordable drugs.

References
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In anticipation of a continued surge in the development of cutting-edge medical treatments, FDA officials are strategizing how the agency assesses and reviews these products. This involves expanding the cadre of experts tasked with evaluating innovative cell and gene therapies, clarifying policies governing this field, and promoting new production methods that support innovation. FDA estimates that sponsors and investigators will file more than 200 investigational new drug applications (INDs) for these products by 2020, adding to the more than 800 applications currently on file for cell-based or directly administered gene therapy applications. FDA predicts that this pipeline will lead to the approval of 10 to 20 new products in this area by 2025 (1). Analysis by academics and research organizations are similarly enthusiastic. The MIT Focus Project, which seeks to devise new methods to pay for innovative, but costly, cell and gene therapies, predicts the approval by 2030 of 40–60 important curative treatments in this area, which will reach approximately 50,000 patients and cost more than $200 billion a year (2).

These advances reflect a “turning point” in the development of this new technology, observed FDA Commissioner Scott Gottlieb and Peter Marks, director of the Center for Biologics Evaluation and Research (CBER)(1). Their information aims to update the biomedical research community on agency initiatives designed to encourage research and development in this area. They note similarities to the acceleration in discovering antibody drugs in the 1990s, citing the importance of developing safe and effective vectors for delivering gene therapies to patients in enabling further discoveries.

A specific plan is to add 50 reviewers in the coming years to expand the staff of CBER’s Office of Tissues and Advanced Therapies (OTAT) and related offices. Additional guidance documents will further advance innovation in this area. FDA plans to outline how sponsors may use expedited review programs, including the regenerative medicine advanced therapy (RMAT) designation and accelerated approval programs, to facilitate the development of gene therapy products that offer meaningful improvements over available treatments for serious or life-threatening conditions. New guidance on developing gene therapies will target neurodegenerative disorders and on inherited blood disorders such as hemophilia. With accelerated approval approaches, FDA also will require post-market, follow-up studies to assess risks and possible side effects that cannot be determined prior to approval.

ADVANCED MANUFACTURING KEY

A critical challenge, add these FDA leaders, is to address the “complexities associated with manufacturing these products in a safe, reliable, and cost-effective way.” Gottlieb and Marks are concerned that sponsors may avoid implementing innovative manufacturing processes for fear regulators will demand additional clinical trials, which are sometimes required with post-approval changes and create additional costs. Guidance that promotes a better understanding of the critical quality attributes and other factors related to product manufacturing of CAR-T and other cellular therapies will aim to clarify what are minor and major manufacturing changes and explain how innovators may adopt advances in manufacturing without the need to confirm safety and quality in additional clinical investigations.

Further guidance documents will examine when minor manufacturing changes can be made....
FDA provided further details in February 2019 on how manufacturers may use expedited development programs for regenerative medicine therapies, clarifying that the category includes gene and Chimeric antigen receptor T cells (CAR-T) therapies, as well as cellular and tissue products. These innovative treatments may qualify for breakthrough status and the regenerative medicine advanced therapy (RMAT) designation, if found to treat serious or life-threatening conditions that lack current treatment.

The guidance from the Center for Biologics Evaluation and Research (CBER) outlines the process for qualifying for RMAT status and what evidence is necessary to gain the designation (1). CBER encourages product sponsors to engage review staff early in development to discuss issues related to pharmacology and manufacturing, as well as pre-clinical and clinical trial approaches.

In addition, a second guidance discusses a range of medical devices that may be used in conjunction with a regenerative medicine product (2). This may include low-risk surgical instruments for recovering cells and tissue, or more complex cell collection and processing systems. The document clarifies current premarket development pathways and when a device and regenerative medicine could be considered a combination product.

References

without additional bridging studies and where limited bridging studies and additional real-world data may be sufficient to document the safety and effectiveness of treatments following production changes that implement advanced technologies. FDA plans to hold a public meeting for agency and industry experts to discuss further ways to expedite bridging studies when more than minor changes are made in manufacturing processes, but those changes fall short of fundamental product transformation.

At the same time, FDA officials look to crack down on organizations and clinicians administering gene therapies not vetted by the agency and thus raising serious safety concerns. FDA intends to expand enforcement actions to rein in manufacturers that fail to comply with regulatory policies. Additional guidance from the agency, moreover, will seek to encourage compliance by small firms and academic investigators by outlining innovative trial designs that permit researchers to pool clinical data for products using a common manufacturing protocol and product quality specifications.

References
Contract manufacturing organizations (CMOs) are on the constant lookout for better single-use systems for their clients. By a relatively wide margin, CMOs have implemented novel single-use systems sooner than therapeutic developers (innovators). This is because CMOs stay competitive when they produce biologics, particularly for R&D and clinical trials, more efficiently and cost effectively (1).

For example, in BioPlan Associates’ 15th Annual Report and Survey of Biopharmaceutical Manufacturing, which included responses from 222 biopharmaceutical manufacturers and CMOs in 22 countries and 130 bioprocessing suppliers or vendors, tangential flow filtration devices are used by 94% of CMOs but only 73.9% of the biotherapeutic developers (Figure 1). Similar results are shown for novel devices such as membrane adsorbers, disposable chromatography, and perfusion devices.

BioPlan surveys conducted during the past 15 years have found the trend of adopting single-use equipment continues, with CMOs leading the way. Single-use equipment, particularly for upstream manufacture (e.g., bioreactors), now dominates small- to mid-scale, R&D, and clinical trial manufacture, while fixed stainless-steel equipment continues to dominate commercial manufacturing.

TOTAL CAPACITY FOR SINGLE-USE DEVICES

In the BioPlan survey, respondents were asked about the adoption of SUS and about facilities’ total single-use capacity. In volume, 17% of respondents noted that their largest single-use bioreactor capacity was 1000 L, suggesting late-stage clinical or commercial manufacturing, and 2000 L was the maximum at 14% of facilities. Approximately one-third of respondents reported facilities had single-use bioreactors with more than 1000 L capacity (i.e., working at large scale by single-use standards). As expected, few facilities (2.3%) had single-use bioreactors with greater than 2000-L capacity. However, this percentage is expected to increase in coming years.

Few mainstream commercial mAb products are manufactured using single-use bioprocessing systems. This is expected to change, however.

Currently, 500–2000 L is often cited as the optimal or most cost-effective bioreactor size for pre-commercial-scale manufacture in mammalian systems, including monoclonal antibodies (mAbs). This range allows for the use of single-use equipment. But single-use equipment has only begun to be adopted for commercial product manufacture, and the current scale for SUS bioreactors, generally limited to 2000 L, is still too small for most commercial antibody production, unless multiple bioreactors are used. While a few facilities, especially
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CMOs, run multiple 2000-L bioreactors together, large-sized fixed stainless-steel equipment continues to dominate commercial mAb manufacture.

Few mainstream commercial mAb products are manufactured using single-use bioprocessing systems. This is expected to change, however, over the next few years as products currently in the development pipeline using smaller scale single-use systems are approved and enter the market. To get there, FDA and regulatory agencies in developed countries will need to see that product manufacturing using single-use devices is safe, and that mAbs produced this way can be comparable to traditional mAb products. Further, many in the industry continue to expect that manufacture in stainless tanks will generally be more cost effective for large-volume liquids.

**SINGLE-USE CAPACITY GROWTH AMONG CMOs**

A growing number of established mainstream bioprocessing CMOs worldwide—and especially in the United States and Europe—are adding commercial manufacturing capacity involving single-use bioreactors in the 1000–2000-L or greater range, generally in one or more 2000-L bioreactor-based process lines (Table I). In addition, specialized CMOs are bringing cell-and gene-therapy facilities online.

Only a few years ago, the industry could boast of single-use bioreactor sizes up to only 1000 L. Now most companies offer bioreactor sizes up to 2000 L, and some are offering 4000-L single-use bioreactors.

CMOs are generally involved with more diverse products than innovator companies, and generally prefer single-use systems for the flexibility and fast changeover time. In addition, the full cost is often passed on to the client. But CMOs are reporting more issues with purification than developers. Innovator companies generally have more time and latitude to optimize downstream bioprocessing, because they develop and scale-up fewer products in-house; development time can be a decade or more. It is not surprising that CMOs responding to the BioPlan

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**Table I.** Recently announced US and European Union contract manufacturing organization single-use commercial-scale expansions and new facilities.

<table>
<thead>
<tr>
<th>Company</th>
<th>Main location</th>
<th>Expansion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fujifilm Diosynth</td>
<td>College Station, TX</td>
<td>12 x 2000 L</td>
</tr>
<tr>
<td>Patheon/Thermo-Fisher</td>
<td>St. Louis, MO</td>
<td>12 x 2000 L</td>
</tr>
<tr>
<td>WuXi Biologics</td>
<td>Dundalk, Ireland</td>
<td>24 x 2000 L</td>
</tr>
<tr>
<td>WuXi Biologics</td>
<td>Worcester, MA</td>
<td>2 x 2000 L; 1 x 500 L perfusion</td>
</tr>
<tr>
<td>AGC</td>
<td>Copenhagen, Denmark</td>
<td>7 x 2000 L</td>
</tr>
<tr>
<td>AGC Biologics</td>
<td>Berkeley, CA</td>
<td>2000 L</td>
</tr>
<tr>
<td>AGC Biologics</td>
<td>Bothell, WA</td>
<td>&gt;2000 L (est.)</td>
</tr>
<tr>
<td>AGC Biologics</td>
<td>Chiba, Japan</td>
<td>2000 and 500 L bioreactors; number of each not cited</td>
</tr>
<tr>
<td>Xcellerex/GE</td>
<td>Cork, Ireland</td>
<td>4 x KuBio modular/SUS facilities (GE to operate for 4 cos.)</td>
</tr>
<tr>
<td>Lonza AG</td>
<td>Singapore</td>
<td>4 x 2000 L</td>
</tr>
<tr>
<td>Avid Bioservices</td>
<td>Tustin, CA</td>
<td>4 x 2000 L (est.)</td>
</tr>
<tr>
<td>Rentschler Biotechnologie GmbH</td>
<td>Laupheim, Germany</td>
<td>2 x 2000 L; 2 x 1000 L</td>
</tr>
<tr>
<td>Sartorius Stedim Cellca (BioOutsource)</td>
<td>Ulm, Germany</td>
<td>5000 L (est. total)</td>
</tr>
<tr>
<td>BioInvent International AB</td>
<td>Lund, Sweden</td>
<td>2 x 1000 L, also 200 L and 50 L</td>
</tr>
<tr>
<td>Oncobiologics</td>
<td>Cranberry, NJ</td>
<td>2000 L; 200 L</td>
</tr>
<tr>
<td>Avantor</td>
<td>Bridgewater, NJ</td>
<td>2200 L total</td>
</tr>
<tr>
<td>Celonic AG</td>
<td>Basel, Switzerland</td>
<td>2000 L; 200 L</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>~150,000 L</td>
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</table>

Source: BioPlan Associates, Inc. resource website www.top1000bio.com
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survey generally expressed higher interest than developers in single-use products, because single-use equipment provides the flexibility and rapid turnaround they require.

SINGLE-USE AND MODULAR MANUFACTURING

Single-use equipment and manufacturing technologies continue to improve, and more modular bioprocessing facilities are entering the market. These advancements are enabling developing regions—such as Brazil and Thailand—to increasingly manufacture for their own domestic needs including commonly used vaccines with or without the participation of original product developers and current manufacturers. Cuba has been manufacturing diverse biopharmaceuticals for itself and international commerce for some time.

Accommodating multiple products in a single plant is a typical way to increase facility utilization, and single-use technologies such as disposable buffer/product bags, drug substance bags, and flow path assemblies for chromatography and ultrafiltration/diafiltration enable quick transition from product to product.

In addition, a facility designed as a shell with reconfigurable space, similar to a nonclinical pilot plant, allows rapid reconfiguration to accommodate a wide range of process sequences. To achieve this, the processes, equipment, and automation must be designed to be highly productive in small, portable modules that can be easily rearranged to enable rapid changeover. Modular designs are enabling plant operators to easily switch between different types of equipment to make different products. Combined modular and single-use technologies reduce investment and operating costs, as well as the financial risk of building new manufacturing facilities. The benefits of this approach, including enhanced quality control, reduced waste, reduced impact on current operations, and simplified site logistics, are leading to a significant change in the design of the next generation of manufacturing facilities.

Future opportunities to expand the application base for single use will arise with the introduction of new therapeutic modalities.

Improvements are expected in the physical/mechanical properties of single-use products and how these products are manufactured and supplied, with a deeper understanding of how they interact with processes and ultimately with patients. These improvements will occur not just for bioreactors but for other critical components like flow paths, filtration, and chromatography, which still lag behind cell culture in terms of capacity. Future opportunities to expand the application base for single use will arise with the introduction of new therapeutic modalities or novel ways of manufacturing established products. Cell culture-based vaccines, highly potent antibody-drug conjugates, bispecific antibodies, antibody fragments, and gene and personalized therapies will involve unique production challenges.

Single-use systems can provide cost savings; sometimes these savings can be substantial compared with fixed stainless-steel systems, particularly larger systems. However, as in previous surveys, direct cost savings did not appear to be the primary factor for decision-makers. The data indicate that users of disposable systems are as concerned or more concerned about factors that will save time (add speed), reduce risk and processing disruptions, increase flexibility, and accelerate campaign turnaround. They are also interested in reducing capital equipment.

As the industry matures, vendors are introducing technologies such as improved single-use films/bags, sensors, chromatography systems, and mixers to differentiate themselves from the competition. This bodes well for customers, as competition may drive down prices and create more options to choose from. Recent advances continue in the area of single-use bioreactors where the size and scale of the vessels are increasing along with their automation.

Single-use systems can save on facility and campaign costs for CMOs, which in turn can reduce operating costs and capital investments. The flexibility and quick turnaround times between process runs and client projects allowed by single-use equipment can also improve efficiency, which can reduce costs. These savings can be passed on to clients and, ultimately, to patients. Such savings also increase the perception of the cost-savings associated with contract manufacturing and potentially increase CMO profits.

REFERENCE

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Considering Alternative Dosage Forms for Biologics

Optimizing the patient experience and technological advances can positively impact adherence.

FELICITY THOMAS

The global biopharmaceutical market is projected to experience significant growth in coming years (1). An aging population, increasing prevalence of chronic conditions, rising proportion of obesity amongst the global population, and more sedentary lifestyles have all been noted as contributing factors to the increasing demand in biopharmaceuticals.

Biopharmaceuticals are also known to offer great efficacy and safety for a number of illnesses that were previously thought to have been untreatable (2). However, it is also widely understood that biopharmaceuticals present specific challenges during drug development and finished dosage form production, as a result of the complexity, sensitivity, reactivity, viscosity, and expense of these macromolecules.

In general, to overcome the formulation and bioavailability challenges associated with biopharmaceuticals, administration is, more often than not, performed via a parenteral (e.g., intravenous infusion or injection) usually given by a healthcare professional. As biopharmaceuticals are often used in the treatment of chronic conditions, however, administration of treatment is required at regular intervals over a long period of time (3). Therefore, the potential treatment burden of biopharmaceuticals can have a negative impact on patient experience and adherence rates. An industry viewpoint, which is becoming increasingly popular, is that patient-centric approaches to drug development are conducive to a more commercially successful outcome for a therapy (4).

“Of note, a survey conducted by eyeforpharma in 2014 (5) revealed that 86% of pharma executives feel that patient-centric drug development is key to profitability, with benefits increasingly recognized by patients and payors,” states Jessica Rousset, chief operating officer, CURE Pharmaceutical. “Alternative dosage form strategies, such as replacing an injection with a transdermal patch or metered dosing, align fully with the trend toward personalized medicine.”

OPTIMIZING THE PATIENT EXPERIENCE

“Biopharma and pharma companies often develop alternative dosage forms to optimize the patient experience, such as
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parenteral dosage form for subcutaneous administration,” explains Matthew Huddleston, executive vice-president and chief technology officer, Enable Injections. He highlights the example of the Enable enFuse injector, which comprises a bolus injector and infuser. “This infusor was designed to optimize the patient experience by enabling patient self-administration of high-volume therapeutics outside of a healthcare facility,” he notes.

“Patient acceptability of a medicinal product is a key aspect in the development of medicines,” adds Rousset. “Developers typically consider alternative dosage forms with patient experience and population in mind. Considerations such as patient population age, disease state mobility, and body function are drivers.”

Huddleston concurs that additional care during the development of alternative dosage forms should be taken depending on the target patient population. “Ease-of-use and the physical limitations of the patient can be a major factor in the development of drug-device or biologic-device combination products,” he says. “For example, pediatric patient populations may have device size or dose limitations based on age, whereas geriatric patients may have hand dexterity limitations during drug administration.”

Hanns-Christian Mahler, head of Drug Product Services, Lonza Pharma & Biotech, further emphasizes the point that development of any given drug product must carefully and closely consider both the target indications and patient populations. “This consideration should relate to possible variability in a given patient population, but should also reflect patient preferences, duration of drug use (acute vs. chronic), required co-medications, and other factors,” he says.

**BENEFITS OF ALTERNATIVE DOSAGE FORMS**

Assessing the role of delivery systems to improve biologics therapy, alternative routes of administration could greatly benefit many biologics, reported Nataša Škalko-Basnet (professor and head of the Drug Transport and Delivery Research Group, Department of Pharmacy, University of Tromsø, Norway) in a 2014 paper (6). Yet, the unique features of biologics have led to challenges during formulation development, with most strategies employed for small-molecule compounds being non-transferable to the large-molecule arena.

As biologics are more often delivered via the parenteral route, which features specific limitations in terms of product development (6), alternative dosage forms could offer developers opportunities in terms of logistics and user experience, Mahler stresses. “Alternative dosage forms for biopharmaceuticals may provide opportunities to allow biologics to be stored, shipped and used outside 2–8 °C, facilitating supply chain,” he says. “And, it may be possible to also improve the user experience— for example, by using better needles or devices for parenteral administration and/or exploring non-parenteral administration routes such as oral, pulmonary, rectal, or vaginal administration.”

Choosing an alternative dosage form can positively affect medication adherence as well, particularly when improvements in the patient experience are gained, concurs Rousset. “Improvements can be made by replacing an injectable drug with a sublingual drug, simplifying the dosing schedule with a sustained release dosage form, and reducing toxicities by avoiding the GI tract (e.g., through transdermal or transmucosal delivery),” she notes. “For all these solutions, developers must put consumers directly at the center of the business.”

A supplementary advantage of alternative dosage forms may be present in accelerated and less costly regulatory pathways, Rousset adds. “Companies that change the dosage form of an approved drug may pursue the regulatory 505(b)(2) approval pathway, which relies on existing data, thereby saving time and expense, while maintaining market exclusivity for three to as many as seven years,” she notes.

Furthermore, Rousset explains that intellectual property benefits may be achieved when developing an alternative dosage form. “The patent landscape around alternative dosage forms may be less crowded, resulting in a lower barrier to entry to develop and commercialize drug product,” she says. “In the event that less prior art is directed toward an alternative dosage form, the time and cost of obtaining new patents of decent claim scope on a drug product in such dosage form can be reduced, with an opportunity to create a patent ‘thicket’ and further market exclusivity.”

**CHALLENGES FACING DEVELOPERS**

The economic burden of research and development of a new molecular entity (NME) is well known. In a paper published by the Office of Health Economics (OHE) (7), it was noted that mean estimations of R&D cost should be treated with caution but that the most important factors impacting cost are therapeutic area, firm size, type of molecule (traditional vs. biologic).

Based on the estimates in the OHE paper, however, it was deemed that R&D costs are increasing partly driven by more complex disease targets and the trend toward personalized medicine (7). Biologics and biopharmaceuticals were subject to longer development times and higher costs per approved new molecule. Yet, the authors of the study also found that the estimated overall clinical success rate for biological products
was higher than that for other traditional pharma products.

In terms of developing alternative dosage forms, associated cost implications ranked highly by Rousset, Huddleston, and Mahler. “With innovation comes risk, and so alternative dosage forms must overcome challenges such as an uncertain regulatory pathway and unproven technologies that can, at times, fall short or be costlier,” notes Rousset. “There may be a higher bar to pass with the regulatory agencies if they are not familiar with a certain dosage form, and they may require multiple additional studies for approval.”

Costs may also be incurred during the initial formulation or product development stage, adds Huddleston. “Further cost challenges may arise as a result of delays or extensions to timeframes due to stability testing programs, unforeseen impacts on drug safety and/or efficacy, and the potential introduction of new use errors identified due to a novel user interface and human factor challenges,” he says.

For Mahler, two main challenges face developers in terms of non-parenteral administration of biologics—risk of degradation of the biologic and lower bioavailability—giving rise to costlier products. “First, the size, charge, and poor stability of biologics products render them very susceptible to degradation when administered non-parenterally,” he explains. “For example, upon oral administration, biologics will be exposed to harsh pH conditions that will destroy the biological active ingredient in vivo.

“Secondly, the size and charge of biologics mean poor biological membrane permeation. However, transfer via biological membranes is required for any non-parenteral administration where systemic exposure of the drug is desired. Thus, biologics have very poor bioavailability, if being absorbed at all. Low bioavailability means a higher amount of drug must be dosed, which leads to significantly higher cost of goods,” he stresses.

Finally, Rousset states that when an innovative dosage form makes it to commercial launch, there may be challenges surrounding adoption by patients, payers, and clinicians. “Humans have a natural tendency to go with what they know and trust,” she says. “New dosage forms must demonstrate clear patient benefits and be introduced at an optimal price point to ensure market adoption.”

Contin. on page 50
The Expanding Landscape of Commercial Single-Use Bioreactors

The following takes a look at recent investments by contract manufacturers to increase single-use bioreactor capacity.

FELIZA MIRASOL

The continued adoption of single-use bioreactors in the biopharmaceutical industry is growing, with several companies making the move to expand implementation of commercial-scale single-use bioreactors. WuXi Biologics, a contract development and manufacturing organization (CDMO) and part of WuXi AppTech, has announced a slew of investments showing its build-up of single-use bioreactor capacity. AGC Biologics, a full-service provider, and ABEC, a contract manufacturer, have also announcement investments in expanding their manufacturing capacities.

COMMERCIAL EXPANSION

WuXi Biologics, a CDMO and part of WuXi AppTech, has been active in expanding its bioreactor capacity with several investments over the course of the past year. The company has been making multi-million-dollar investments into implementing these expansions.

The largest of these recent investments is a €325 million (US$370 million) investment announced on April 30, 2018 (1). The company is using the investment to build a new biomanufacturing facility in Mullagharlin, Dundalk, County Louth, Ireland. The new facility will use multiple single-use bioreactors for commercial biomanufacturing and is designed to be able to run continuous bioprocessing. A total of 48,000-L fed-batch and 6000-L perfusion bioreactor capacity will be installed.

The Ireland facility marks the first manufacturing site that WuXi will have outside of China. The project is expected to create more than 400 skilled jobs over a five-year span and add approximately 700 construction jobs.

Following the Ireland facility announcement, WuXi reported a S$80 million (US$60 million) investment in May 2018 to establish a biologics manufacturing facility in Singapore (2), its tenth global drug substance manufacturing facility. The Singapore site represents the company’s second site outside of China and its first in Asia that is outside of China.

This facility will house single-use bioreactors with a total of approximately 4500-L bioreactor capacity that will be installed with two 2000-L traditional fed-batch and one 500-L perfusion-based continuous processing bioreactors. The facility will handle both clinical and small-volume com-
mmercial production. The site will also house an early-stage bioprocess development laboratory. The investment will provide approximately 150 jobs.

In the United States, WuXi is also investing $60 million to establish a biologics clinical and commercial manufacturing facility in Worcester, MA. The company announced this investment in June 2018 (3). This US site will be the company’s eleventh global drug substance manufacturing facility and its first in the US.

The Worcester facility will also house single-use bioreactors and will be designed to run continuous bioprocessing. The company plans to install a total of approximately 4500 L of bioreactor capacity using two 2000-L traditional fed-batch bioreactors and one 500-L perfusion-based continuous process bioreactor.

Similar to the Singapore facility, the Worcester facility will handle both clinical and small-volume commercial production, and the company will include an early-stage bioprocess development lab as well. The site will provide positions for approximately 150 employees.

CAPACITY BUILDUP
These 2018 announced investments follow a larger earlier investment the company made in April 2015. At that time, WuXi announced a $150-million investment to build a new 30,000-L cGMP biologics manufacturing facility in Wuxi, China. That facility started up operations in early December 2017 and is now fully operational (4).

The Wuxi facility houses two 1000-L disposable perfusion-based bioreactors and 14 2000-L disposable fed-batch cell culture-based bioreactors. The 500,000-ft² facility quintuples the company’s existing manufacturing capability and supports the biologics commercial manufacturing pipeline coming from the company’s global partners.

The company also announced in March 2018 that it plans to install 4000-L custom single run (CSR) disposable bioreactors supplied by ABEC, a provider of integrated process solutions and biopharmaceutical manufacturing services, at the new Wuxi facility (5).

This 4000-L CSR bioreactor is the largest single-use bioreactor size available in the industry today and is potentially the largest design in conventional disposable bioreactors, according to WuXi. The system can be fully customized for different products, the company reports. The company’s scale-out strategy involves using multiple 4000-L CSRs for commercial manufacturing, which would enable production up to a scale of 24,000 L, comparable to stainless-steel bioreactors.

In a similar move to grow its manufacturing capacity, AGC Biologics, a CDMO, is adding a 2000-L single-use bioreactor to its Berkeley, CA, facility to support its biologics capacity. The company announced the addition in March 2018 (6). The Berkeley facility is one of six facilities that AGC runs worldwide. The company has tripled capacity at its Berkeley site over the past three years. The facility uses both single-use and stainless-steel bioreactors for cell culture manufacturing in scales from 100 L–3000 L. The facility provides cell bank manufacturing and storage.

AGC Biologics is a recent integration of Asahi Glass Company (AGC) Bioscience, a glass and chemical producer under AGC, Biomeva GmbH, a contract manufacturing organization, and CMC Biologics, a contract biologics manufacturer. AGC Biologics was formed in January 2018 (7).

LAUNCH OF THE 4000-L BIOREACTOR
The 4000-L-scale single-use bioreactor was launched by ABEC in July 2017 (8). The company noted that it is the only supplier that today can provide single-use bioreactors with capacities greater than 2000 L.

Benefits of the 4000-L single-use bioreactor include a reduction in capital, facility, and disposables cost by doubling cell-culture capacity in approximately the same floor space. In addition, the capacity of the vessel can lead to a reduction by half of the number of systems and disposable containers needed, which in turn can mean a reduced-size facility, according to ABEC.

Performance of the 4000-L bioreactor is comparable to that of stainless steel systems, which figure prominently in the company’s CSR product line. Other features of the line include large production volumes, seamless process transfer and scale-up, rapid container loading, and a non-proprietary supply chain.

REFERENCES
Membrane Technology for Enhancing Separation and Purification

Downstream process equipment for mAbs manufacturing must be designed to fit technology developments in upstream processes.

FELIZA MIRASOL

Downstream separation and purification remains challenging in the manufacture of monoclonal antibodies (mAb). One way that suppliers are tackling this challenge is through the development of innovative membrane technology. *BioPharm International* discussed past and current innovations in membrane technology with Gabriel Tkacik, the director of Filtration R&D at MilliporeSigma.

**INNOVATIONS IN UPSTREAM AND DOWNSTREAM**

**BioPharm:** What currently are the key challenges in the downstream separation and purification process for mAbs?

**Tkacik:** After 20-plus years of a standard manufacturing template for mAbs, we are seeing an evolution towards more intensified processes, which means that current templates can range from standard batch to fully flow-through continuous processing. Fluid streams from intensified processes may be more concentrated than batch streams, which can result in higher viscosity and impact the efficiency of processing. The range of operating conditions and processing times of continuous processes are likely to be different from those of batch processes for which current technologies were designed. Maintaining efficiency while controlling costs under these different processing conditions is a challenge for every operation.

From a device perspective, one clear challenge for many operations is the loss of process fluid in a device, which is referred to as ‘dead’ or ‘hold-up’ volumes. This is especially important for higher concentration fluids, where high hold-up volumes have a greater impact on yield and process economics. Another challenge is maintaining the integrity of the material, through connected operations, in a ‘closed’ flowpath. Closed processing offers manufacturers greater flexibility, minimizes changeover cleaning requirements, and reduces the risk of product contamination by limiting microbial ingress.

Considering individual unit operations for separation, reducing impurities and particulates from fluid streams remains a challenge. These can come from the cell culture process or they can be high-molecular-weight aggregated forms of the target protein, which tend to form at higher protein concentrations. As target molecules have been engi-
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For efficient processing of feed streams with higher particulate concentrations, we have moved away from a one-size-fits-all membrane filter to more specialized membranes for specific operations. For efficient processing of feed streams with higher particulate concentrations, high-area filters have been developed that contain prefilters and sterilizing-grade membranes packed in a single device and are designed to maximize membrane area in a smaller filter footprint than standard filters.

For tangential flow filtration, the challenges of product loss in device dead volume accelerated development of more efficient membranes that enable higher flux processing for a given cross-flow in single-use devices with limited dead volume. These devices result in more consistent, reliable performance. Similarly, processing efficiency of virus retentive membrane filters has been improved by the development of specialized membrane prefilters that operate under specific pH and conductivity conditions to separate protein aggregates from monomers, thus improving filterability.

In terms of biosafety, the focus on risk analysis has highlighted needs of differentiated separation technologies for microorganism retention at different process steps. Where once sterilizing-grade membranes might have been used throughout upstream and downstream processes, specialized virus-retentive membranes have been developed for processing cell culture media to reduce the risk of adventitious virus and more challenging microorganisms contaminating bioreactors and cell-culture processes.

For downstream operations, where many steps are considered ‘low bioburden,’ rather than truly aseptic, membrane filters that offer bioburden reduction rather than sterilizing-grade performance have been developed as a cost-effective alternative to reduce microbial risk.

“For novel therapies, there is a real need for innovative membrane technologies to enable efficient processing.”

—Gabriel Tkacik, MilliporeSigma

Major technical advances have been made in purification technologies to meet the desire of manufacturers to move to more flexible single-use templates. Development of single-use membrane technologies, which can be run in flow-through mode or rapidly cycled, offer opportunities to replace traditional resin-based purification operations. These newer membrane technologies offer both flexibility and operational efficiency and increase options for manufacturers.

BioPharm: What challenges does continuous processing pose to the way membranes must be used or how they need to perform?

Tkacik: Continuous processing conditions can be quite different to batch operations and generally are of longer duration, perhaps weeks as compared to hours for typical batch processes. This extended duration heightens the need for tight bioburden control; gamma pre-sterilized devices are needed, as are tools for sterile sampling and collection. The separation and purification technologies should also maintain performance during flow or process interruptions that are likely to occur during long-duration processes. Devices for use in continuous processes should be designed to enable sample collection without compromising the sterility of the fluid flowpath and should be easily integrated into single-use systems. As with many major shifts in technology, continuous processing presents another challenge: should we reconsider how we validate filter performance during these operations?

FUTURE DEVELOPMENTS

BioPharm: What objectives or performance criteria should newer membrane technologies strive for?

Tkacik: Newer membrane technologies need to be ready for tomorrow’s processes, which are likely to increase in diversity as manufacturers fit processes to meet the needs of their facility, scale, and the API being produced. Manufacturers are developing processes for more complex and diverse molecules than ever before and need efficient separation and purification for fluid streams of both high and low concentrations, in batch and continuous operations, with closed processing options and flexibility for rapid setup and changeover. These options will ideally reduce risk of product and operator contamination, be easy to use, and be reasonably priced to work in the cost framework of manufacturing operations. For mAb operations, the portfolio of product offerings is extensive, but for novel therapies, there...
is opportunity for novel or improved membrane technologies to simplify production and increase accessibility to these novel therapies.

“From a device perspective, one clear challenge for many operations is the loss of process fluid in a device.”

—Gabriel Tkacik, MilliporeSigma

**BioPharm:** In what aspect(s) is current membrane technology still lacking (i.e., where is there still need for improvement)?

**Tkacik:** For mAb separation and purification technologies, the development of ‘SMART’ membrane technology that could provide real-time processing information and potentially alert operators in the event of excursions would add a level of control not available today. Ideally, data would be automatically collected into the batch records.

For both separation and purification membranes, the availability of more accurate scaling tools that can better predict the sizes or area requirements of the full-scale process would prevent oversizing or under-sizing devices and the resultant product loss or increased risk that would incur.

For novel therapies, there is a real need for innovative membrane technologies to enable efficient processing: viral vector production processes are challenging separations as the vectors themselves are similar in size to the microorganisms they are being separated from. For novel cell therapy and viral vector processes, membranes that can efficiently filter all cell culture media components might add a level of safety assurance to processes with limited options for viral clearance during downstream purification. Purification technologies that could effectively partition the target therapeutic from impurities could streamline production. Understanding the specific needs of these new applications offers suppliers new opportunities for technology development and offers manufacturers the opportunity to work closely with suppliers to design or modify products to meet these needs.◆
Manufacturing

Automating the Biomanufacturing Process

As automation in biomanufacturing becomes more important, so does the need to integrate process data.

FELIZA MIRASOL

Biomanufacturing processes have been automated for years, and use of automation is expected to grow significantly in the near future. As a result, data integration is needed to handle the huge increase in product data from this growth to ensure that these raw data become information that can be used to control and improve the process and product.

AUTOMATION IMPLEMENTATION

For more than 15 years, biopharmaceutical manufacturers have been implementing automation and control systems, both upstream and downstream, says Christoph Lebl, head of Global Automation and Controls, Lonza Pharma & Biotech. Automation has traditionally focused on controlling the manufacturing process throughout production to ensure that product remains identical between batches. Control has been manifested mainly in minimizing manual interactions and preventing operator error, to prevent variability in production and in product quality that would require correction.

Today, he says, automation is poised to play a much more visible role in biopharmaceutical operations, particularly in moving material between sites in the production process. Currently, this is done manually, Lebl says, and this has a direct impact on biopharmaceutical labor costs, which account for 40–50% of production costs, compared with 10–15% in other industries. “A large proportion of this cost goes to having people physically transfer material and products from place to place,” he says. As robotic systems become more accessible and less expensive, Lebl sees them playing a bigger role in pharmaceutical manufacturing, especially for material movement.

Besides data storage, analytics, and generation of process data, especially in single use (SU) processing, sensor incorporation in the biobag design is important. This allows for direct measurements without jeopardizing the sterility of the bag. One supplier has extended and improved its sensor portfolio, by, for example, including a sensor that measures biomass in the United States Pharmacopeia bags used for rocking motion-
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INTEGRATING AUTOMATED SYSTEMS
As the need for data integration increases, it is essential to optimize the flow of data among different automated process lines to ensure that it can be collected and used. “It is crucial to apply the same level of automation and operational philosophy across the entire production, from seed lab to final formulation,” says Lebl.

“It is crucial to apply the same level of automation and operational philosophy across the entire production, from seed lab to final formulation.”
—Christoph Lebl, Lonza Pharma & Biotech

Ensuring traceability is key, he emphasizes. For example, if an equipment component that is used in production is later suspected of having contributed to quality problems with one specific batch, automation systems like manufacturing execution systems (MES) are there that provide the traceability needed, locating the impacted production batch swiftly and mitigating negative impact.

“Experienced manufacturers operate with integrated data systems, so all production data are available in one place. Without an integrated data system in place, it can be nearly impossible to access data quickly to assess whether a batch is on track—and to intervene if it is not,” Lebl says.

Currently, the biopharmaceutical manufacturing and supply chain boasts high levels of integration throughout. According to Lebl, enterprise resource planning (ERP) systems encourage dialogue between warehouse and shop floor to ensure on-time material consumption and production. “Integrated systems help deliver the right materials to the floor in the right quantity to match the needs of the customer in terms of drug product delivery,” he states.

However, Lebl sees a need for better automated integration of operator training, for real-time verification to ensure that training is up to date. Currently, he says, this is typically done manually. Another highly manual process today is scheduling. It is in many cases based on paper, relying on humans to connect the performance data from the equipment with planned adjustments.

Smart modular data integration packages can be integrated easily and quickly into distributed control system (DCS) and supervisory control and data acquisition (SCADA) systems. This enables faster build up-times and change-overs, and allow the modular skids to be used in flexible manufacturing, according to a supplier. Enhanced speed and flexibility, in turn, reduces capital and operational expenditures (CAPEX and OPEX).

Normally process-related data is gathered and stored on the process management level in a historian, such as OSIsoft PI (PI Process Information system). From this, historical data can be used to perform sophisticated data analytics.

PREDICTIVE TOOLS
After control, the next use for automated system data will be predictive analytics, says Lebl. “This approach can fine-tune the production process, and flag and correct issues before they arise,” he says.

He also sees a growing role for real-time release (RTR), which uses analytics to test batch quality automatically during the production process, which could significantly reduce the time needed for final qualification steps and product release. “RTR entails higher up-front cost for the equipment and start-up/validation, but allows batches to be released much faster with less human intervention,” Lebl says.

[A] real-time monitoring system can extract data and use a statistical model to create user-friendly process trajectories that show process consistency.

The need for integration between and among automated systems also has an impact on data collection and information flow. “One of the most prominent threats vis-à-vis automated production is the potential for compromised data integrity,” Lebl cautions.

When data are shared more openly and automatically, they become potentially vulnerable, he says. To ensure security, therefore, companies are putting much effort into information technology (IT)/operational technology (OT) infrastructure and cybersecurity. “Some pharma companies are teaming up to create standardized approaches to IT/OT network infrastructure design
and setup to prevent unauthorized intentional and unintentional access,” comments Lebl.

**EASING DATA FLOW**

The potential for higher volumes of data collection and the need for more efficient, seamless data flow are challenges that manufacturers face. Service providers will need to incorporate solutions for easing data collection and flow.

“Our ultimate goal is a ‘plug-and-play’ system of automated bioproduction in which vendors, suppliers, and manufacturers all use equipment that ‘recognize’ each other, allowing for simple integration and data sharing,” says Lebl. “At the moment, for each piece of production equipment that we bring online, we need to create customized software and interfaces—that leads to higher costs and longer production time.”

As part of its solutions trouble-shooting, Lonza participates in the BioPhorum Operations Group (BPOG) initiative, a company-to-company consortium that aims to develop best practices and user requirements between manufacturers and supply partners. “As we work to develop consensus around approaches and standards to production, the industry stands to benefit, along with the people we serve globally,” Lebl says.

### Automation Plays Increasingly Important Role in Bioprocessing

Automation is playing an increasingly important role in bioprocessing, including in cell culture processes and biologic fill/finish operations as well as the biomanufacturing process for therapeutic proteins.

In cell-line generation and cell culture, the processes have traditionally relied on long repetitive hours of manual labor, which produces low output and is vulnerable to human error. Automation helps speed up the processes while freeing up technicians to work on other tasks. It also reduces the risk of injury from the repetitive strain associated with continuous manual tasks. Furthermore, robotics can achieve a level of consistency in procedure and sterility that is difficult to achieve (1).

An example of a recent advancement in cell culture automation is the establishment of an integrated high-throughput, automated platform for cell-line development. This integrated approach combines a cell sorter, a clone cell imager, and a liquid handling system, which enables high-throughput screening and a more efficient process for developing cell lines. The integrated process can screen approximately 2000–10,000 clones per operation cycle (2).

In the fill/finish stage of biologic production, automation also lends assurance that sterility can be consistently maintained. The rise of costly biologics over the past 20 years has put greater pressure on fill/finish operations to ensure that quality, safety, and cost efficiency are not compromised at this critical late-stage process (3).

The advancement of automation, including robotics, in the late-stage fill/finish step further reduces the risks of contamination. Most systems today, not including small manual operations, are typically highly automated. This setup has led to as few human interactions as possible at that step, including the loading of raw materials, system changeovers, and cleaning (4).

Despite benefits (cost, time, process efficiency, consistency, etc.) that automation can provide in bioprocessing, however, adoption of automated technologies is still challenging. Manufacturers, equipment suppliers, and software developers face integration hurdles, regulatory challenges, and a lack of industry-wide standardization. Expectations remain high, however, that solutions to these hurdles will come to fruition within the next 10 years (5).

Furthermore, integrating automated technology becomes more of a challenge as the system or bioprocess itself becomes more complicated. There is a need for greater effort to define, implement, and ensure that automation works correctly within a complex manufacturing process. The challenge of aligning a supplier’s process automation concept to that of a facility automation concept in terms of environmental monitoring, building monitoring, and a certain level of integration into resource planning systems, is also important to consider (5).

### References


—Feliza Mirasol
Further, process historians are needed to store and transfer data safely to allow fast and easy evaluation of data within past and current batches, and to allow comparisons between batches, a supplier adds. For example, a real-time monitoring system can extract data and use a statistical model to create user-friendly process trajectories that show process consistency. In this example, operators can use the real-time monitoring system to spot process variance early and perform a graphical root-cause analysis on the plant floor, allowing them to detect the source of the problem. This would thus prevent process deviation and lost batches. Having the ability to do this on the fly allows operators to bring a process back under control before variance can turn into a critical quality process deviation.

Integration of a modular package unit in an automation landscape was a big effort in the past. The introduction of classical open platform communications (OPC) has been partly simplified integration. OPC unified architecture (UA) is being implemented as the next generation in integrated automation infrastructure, more so for modular package units and SCADA and DCS systems nowadays, according to a supplier.

Though classical OPC and OPC UA provide a good backbone for data transfer, there remains little standardization on the content provided, the supplier points out.

Several working groups are currently working on standards and definitions for interfaces for modular package unit and SCADA/DCS systems. These initiatives have the common goal of improving interoperability of modular package units to SCADA/DCS system, to reach integrations with reduced effort, to enable reduce factory build-up times, and to enable fast changeover between processes, the supplier says.

In addition to BPOG’s work, the International Society for Pharmaceutical Engineers, the Standardization Association for Measurement and Control in Chemical Industries, and the German Electrical and Electronic Manufacturers’ Association (abbreviated NAMUR and ZVEI, respectively in German), are collaborating on modular systems and are working on various plug-and-manufacture approaches.

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In December 2018, FDA published the long-awaited Data Integrity and Compliance with Drug CGMP—Questions and Answers Guidance for Industry. The document provides clarification on how data should be captured to most effectively preserve its integrity, primarily in the current good manufacturing practice (CGMP) regulated space (1).

The document also highlights how organizations are increasingly moving to new, paperless environments, with much of their data now captured using electronic systems. Because of this change, many organizations are subsequently adapting and adjusting their working practices—which were acceptable when paper was being used to record the primary data—to make sure that the requirements of ALCOA (Attributable, Legible, Contemporaneous, Original, and Accurate) can be met.

CHANGING WORKING PRACTICES AND REGULATIONS
One example from FDA’s guidance document describes the use of shared login accounts. Previously, shared accounts have been used to conveniently access a range of computerized systems. In the past, this practice was generally accepted because the data that were being captured were initially written or printed out and then stuck into a paper laboratory notebook, which was assigned to a specific user and defined as the source of the data. But as organizations have moved to new systems where all of the data are captured and documented electronically with the use of software such as electronic laboratory notebooks (ELNs) and laboratory information management systems (LIMS), the expectations of both organizations following the regulations and the agencies generating the regulations have changed.

The main reason for this is the ‘extra’ information and workflow processes that the electronic systems can easily provide over paper when configured and used appropriately. Lots of additional information—like when individual user

SUCCESSFULLY MOVING REGULATED DATA TO THE CLOUD
In light of recent FDA guidance on data integrity, the challenges and benefits of using the public cloud to deploy and use data management software are discussed.

STUART WARD
accounts are used, when data are initially captured by the electronic data management application, details about the user performing the work, and when the work occurred and where it took place—can be automatically captured in a system’s audit trail.

USING TECHNOLOGY TO AUTOMATICALLY FLAG DEVIATIONS

In addition, electronic data management systems can be set up to provide alerts when data entries are not as expected, or when a defined process has been deviations from a defined workflow. This is in addition to the time saving that an electronic data management system can provide by reducing manual manipulations of the data, for example by being directly integrated to the instruments and other systems generating the data instead of having to copy and paste or write the information on paper.

By using electronic data management systems instead of historic paper notebooks, the organizational data review process can be made far easier and much more efficient.

IMPROVING REPORTING USING ELECTRONIC SUBMISSIONS

The other main benefit of electronic systems comes at the reporting stage. If all of an organization’s data has been collected electronically, this can improve the process of reporting to assist with decision making and generation of submissions to the regulatory agencies.

Some regulatory agencies have already expressed their preference for electronic data submissions instead of paper ones, like the Standard for Exchange of Nonclinical Data (SEND) for the presentation of nonclinical data. This is a trend that is only likely to increase as technology becomes more advanced.

Other than reducing the amount of paper that needs to be used, which can often be considerable, electronic data submissions also reduce the need for error-prone manual transcription processes that frequently have to be performed to interpret and review data.

Ensuring data are submitted in a standard electronic format also means that the regulatory agencies can review the data using their electronic tools and processes in a consistent and efficient manner.

But what does this mean in practice? Faster reviews will naturally benefit both the organizations making the submissions and the regulatory agencies viewing the data. But the real benefit is how an expedited submission process can reduce the time it takes to get a new drug to market, which benefits the consumer.

MANAGING EVER-INCREASING QUANTITIES OF DATA

Because electronic systems generally make it easier for users to capture and report on their data compared to paper-based processes, most organizations are now seeing an increase in the amount of data that is being collected and stored within their computerized systems. In turn, with more information available than ever before, regulatory agencies are also demanding more information to ensure they can be confident that the data being collected and reviewed are complete, as demonstrated in the FDA guidance document previously mentioned.

There is an obvious knock-on impact also. Organizations creating more data will need to find an effective way of storing this new and valuable information; for some, this will mean evaluating and ultimately improving the computing infrastructure that they have in place. Historically, companies have provisioned the infrastructure ‘on-premise’ either in a location on-site or in a third-party hosted data centre. Increasing the amount of on-premise computing infrastructure usually means that extra servers need to be purchased, which can take a considerable amount of time and does not necessarily meet the ever-changing needs of the businesses involved.

FINDING NEW, FLEXIBLE SOLUTIONS TO EFFECTIVELY STORE REGULATED DATA

Wary of the limitations of on-premise solutions, many organizations are looking for different ways to run their data management systems with a focus on flexibility to meet the changing needs of their business.

Some are using private or public clouds—which can be scaled to meet demands—for the provision of the computing infrastructure to host the software, or are turning to vendors that provide software-as-a-service (SaaS), which provides the ultimate control when it comes to flexibility by allowing organizations to pay for what they use. As well as providing an environment that can easily be changed to meet the demands of the organization, using the cloud can also have a number of other benefits to the organization producing data for regulated use. In particular, data security, which in turn helps provide data integrity.

THE BENEFITS OF MOVING TO THE CLOUD

A cloud provider will generally have more specialized staff members focused on providing a secure infrastructure when compared to organizations providing on-premise data centres. Because security is a crucial part of a cloud provider’s business model, the increase in staff numbers is expected. Without this emphasis, the cloud would simply not be viable, particularly for scientific domains where data security is of the utmost importance.

Contin. on page 53
Biotherapeutics are an emerging class of treatment modalities that are manufactured using living cells. They have been successfully used for treating many life-threatening and chronic diseases. Compared to the traditional small-molecule (pharmaceutical) drugs, biotherapeutics are complex and have the ability to bind to more than one target molecule. Biosimilars provide a more affordable treatment option, and this is likely to become more relevant in the future as the affordability of these products remains critically poor in emerging and underdeveloped economies (1–3). The biopharmaceutical industry faces an increasing demand to accelerate process development while saving on cost and time. A possible solution to alleviate this is by using high-throughput potential tools such as surface plasmon resonance (SPR) to measure biomolecular interactions in real-time and in a label-free environment (4, 5).

Biomolecular interaction analysis (BIA) can be used in the following ways (3):
• To monitor the level of interactions between two or more species
• To determine the affinity of the interactions
• To estimate the actual association and dissociation rates
• To measure the concentration of one of the species.
SPR is a rapidly emerging tool for studying ligand binding interactions with membrane proteins, which are the major molecular targets for biopharmaceutical products (6). In SPR, one of the interactants is immobilized to the sensor surface and the other is kept free in solution and passed over the surface. Association and dissociation are measured and displayed in the form of a sensorgram. In this 41st article in the Elements of Biopharmaceutical Production, the authors present the basics of SPR as well as the various applications it offers in biopharmaceutical analysis.

**VARIOUS MEASUREMENTS POSSIBLE WITH SPR**

Detection of specificity is comparably easy to perform in SPR. An analyte is injected and, after a certain amount of time, the response is measured. Plotting the response curve against sample number indicates the relative strength of binding. Bulk response caused by the medium in which the analyte is dissolved is the major drawback but can be easily avoided with proper reference measurements (7, 8).

Analyte concentrations are measured at very high ligand densities on the sensor surfaces. The rate of the binding constant is proportional to the concentration of the analytes. After a standard curve has been created, unknown samples can be measured quickly.

Equilibrium analysis is used to determine the strength of the binding. The first type is performed by using several analyte concentrations, which involve flowing the analyte over the ligand until the signal levels out and the net association is equal to the dissociation. By plotting the maximum response versus the analyte concentration, a line can be fitted to estimate the affinity constant (KD). The second type of experiment involves putting the two interactants together and incubating them until equilibrium. One of the interactants is to be constant, and the other is varied over a range of concentration. The concentration of the free analyte can then be determined after equilibrium.

Kinetic rate analysis is used to investigate the behavior of the system. Interaction kinetics describes the interaction between one or more components. After the interaction, the components leave each other unchanged as opposed to enzyme kinetics. The rate of association is determined in real time when the analyte flows over the ligand. Over time, the buffer replaces the analyte and the dissociation rate of the analyte is monitored. Both the association and dissociation curve can be fitted to one of the chosen models. In addition, the equilibrium constant can be calculated (9, 10).

There are two types of experimental approaches available for kinetics experiment: multi-cycle kinetics (classical “standard” approach) and single-cycle kinetics (see Table I).

Various techniques are used to study structure-function affinity. The function is measured in terms of specificity (affinity), rate and equilibrium constants, as well as thermodynamic properties. While with the majority of SPR experiments the interaction conditions are held constant, varying these conditions (e.g., the temperature) can reveal important thermodynamic properties. SPR systems are capable of measuring the specific ligand–analyte interaction in real-time, which enables the researcher to simultaneously estimate both the rate and equilibrium constants (11, 12).

Calibration free concentration analysis (CFCA) has been developed for measuring the active concentration of a ligand without a calibration curve (9). The method makes use of the mass transport limitation, which occurs when high-density ligand surfaces are used. By injecting the analyte at two different flow rates (e.g., 10–90 μl min⁻¹), the active analyte concentration can be calculated from the slopes of the curves (13).

**HOW MUCH LIGAND TO IMMOBILIZE?**

Table II shows the ligand immobilization on the sensor chip are as follows:

- Kinetics should be done with the lowest ligand density, which gives a good response without being disturbed by secondary factors such as mass transfer or steric hindrance.
- For specificity measurements, almost any ligand density will do as long as it gives a good signal.
- Concentration measurements need the highest ligand density to facilitate mass transfer limitation.
- Affinity ranking can be done with low to moderate density sensor chips.

---

**Table I. Multi-cycle and single-cycle interaction kinetics between ligand and analyte determine the injection strategy in an experiment.**

<table>
<thead>
<tr>
<th>Multi-cycle kinetics</th>
<th>Single-cycle kinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analyte concentration series</td>
<td>Analyte concentration series</td>
</tr>
<tr>
<td>Each concentration in a separate cycle</td>
<td>Up to five concentrations in a single cycle</td>
</tr>
<tr>
<td>Multiple dissociation phase</td>
<td>Single dissociation phase</td>
</tr>
<tr>
<td>Zero concentration + replicates</td>
<td>Zero concentration cycle + No replicates</td>
</tr>
<tr>
<td>With capture, new ligand for each cycle</td>
<td>With capture, single ligand injection</td>
</tr>
<tr>
<td>Regeneration requirement</td>
<td>No regeneration</td>
</tr>
</tbody>
</table>

---

**Table II**

<table>
<thead>
<tr>
<th>ligand immobilization on the sensor chip are as follows:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinetics should be done with the lowest ligand density, which gives a good response without being disturbed by secondary factors such as mass transfer or steric hindrance.</td>
<td></td>
</tr>
<tr>
<td>For specificity measurements, almost any ligand density will do as long as it gives a good signal.</td>
<td></td>
</tr>
<tr>
<td>Concentration measurements need the highest ligand density to facilitate mass transfer limitation.</td>
<td></td>
</tr>
<tr>
<td>Affinity ranking can be done with low to moderate density sensor chips.</td>
<td></td>
</tr>
</tbody>
</table>
**Biosimilars**

**Table II.** Ligand immobilization on the sensor chip in different binding patterns in surface plasmon resonance.

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concentration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affinity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kinetics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMW Binding</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1.** Factors that need to be analyzed and controlled for biosimilar development.

- Low molecular mass binding should be done with high-density sensor chips to bind as much as possible of the analyte to gain proper signal.

**ANALYTICAL CHARACTERIZATION AND COMPARABILITY OF BIOThERAPEUTICS**

Biotherapeutics are complex products and, therefore, require characterization using numerous orthogonal analytical tools. Biosimilars undergo limited clinical examination prior to approval under the premise that comparability to the corresponding innovator product using an exhaustive analytical characterization exercise has been demonstrated (14). The comparability exercise involves characterization and analysis by a platform consisting of numerous, orthogonal analytical tools (**Figure 1**). Failing to demonstrate similarity can come at a significant cost and can trigger a more extensive (and expensive) clinical examination prior to receiving regulatory approval. Guidance documents from regulatory health authorities, such as FDA and the European Medicines Agency (EMA), emphasize the importance of extensive analytical characterization in showing the similarity between a biosimilar and its reference product based on a comprehensive assessment of protein structure and function (15, 16). As such, developers of biosimilars must put together a toolbox of state-of-the-art technologies. Companies such as Sandoz and Celltrion, which have both received FDA approvals for biosimilars, have had success in using real-time, label-free biophysical analytics as a platform approach for product and process support, evaluating target and receptor binding, and for measuring immunogenicity and specificity. Another significant challenge with biosimilars as well as other biological products is that of standardizing the Fc receptor binding. Fc receptors can be activating, or inhibitory, or without any effect in antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). Characterizing these highly complex products and their interactions, however, is extremely challenging (13).

Monoclonal antibodies (mAbs) are at present the fastest growing subclass of biopharmaceuticals and have been successfully demonstrated to treat a variety of diseases, mainly in oncology and auto-immune and infectious disease segment. Antibodies recognize their antigen through the variable regions of the antigen-binding portion (Fab). As a result, they may interfere with one or several functions of this antigen, leading to the therapeutic effect. On the other hand, through the constant regions (Fc), they may interact with Fc-binding molecules and recruit patient immune effector function to destroy the marked
target. The ADCC is triggered by an interaction between the Fc region of an antibody bound to, for example, a tumor cell and the Fcy receptors on immune effector cells, leading to the elimination of the tumor cell by phagocytosis or lysis, depending on the type of mediating effector cell. CDC is initiated by complement component C1q binding to the Fc region of the antibody, triggering activation of the complement that leads to cell death by phagocytosis, lysis, or disruption of the cell membrane (16). SPR is a well-established technique for detection and monitoring of biomolecular interactions in real time. It has been formatted as a parallel line assay and researchers have demonstrated high levels of accuracy, precision, and linearity with the assay, making it useful for establishing comparability, estimating potency and examining stability (17–20). SPR has also shown greater precision and reproducibility than the traditional cell-based assays such as ADCC and CDC.

SPR applications are not only limited to ligand–receptor interaction kinetics dynamic analyses, but they are also used for drug discovery and development. There are several different formats of SPR biosensors, including the array format, multi-channel unit format, and SPR imaging format, which allow simultaneous and continuous detection to analyze the performance of hundreds to thousands of affinity binding events on a chip surface. In SPR imaging, the incidence angle remains fixed and the binding of biomolecules on a gold surface is measured as the change in reflectivity in relation to the incident ray intensity, unlike SPR sensors that depend on the measurement of the absorption dip in the SPR angle or SPR wavelength. Despite the excellent benefits inherent in SPR technology, conventional propagating SPR biosensors have a serious limitation due to their inability to support multiplex analysis, as less than four analyses with conventional SPR instruments make such parallel operations feasible. In contrast, SPR imaging technology uses a multi-analyte biosensor that permits a high-throughput approach and achieves a similar degree of sensitivity that is achieved by conventional SPR biosensors. Therefore, SPR imaging systems without any labeling requirements are more suitable for high-throughput screening (HTS), particularly in drug discovery, than any other optics-based detection techniques (21, 22).

Antibody applications of SPR broadly fall into two categories, such as screening and characterization. Antibody screening often involves capture of an antibody followed by a single injection of antigen. The kinetics of binding can be estimated directly from a screening experiment and is of major interest for antibodies intended for diagnostic or therapeutic purposes. Antibodies with slow off rates are often selected as candidates to provide prolonged drug residence time and also potentially higher efficacy (23). A complicating factor in the selection procedures is that antigen binding may be heterogeneous, and such antibodies are often deselected in favor of monophasic binders that may be more specific. The selection is, therefore, focused not only on stable binding but also on monophasic binders. In antibody characterization, SPR is typically used for epitope binding, specificity, concentration, and kinetic/affinity analysis. When using SPR for establishing analytical comparability, the biosimilar product is compared with the reference product.

**BINDING PATTERNS OF SPR**

Antibodies, cytokines, and hormones typically interact with their receptors. While cytokines and hormones retain their natural sequence and folding, antibody therapeutics are engineered to interact with target molecules (including antigens, Fc receptors, and complement factors) based on their intended mechanism of action. SPR data experiments were performed using SPR based sensor system (GE Healthcare) with analysis temperature set to 25 °C. Series S Sensor Chip CM5, Series S Sensor Chip NTA, Series S Sensor Chip Protein A HBS-EP buffer (10 mM Hepes, 0.15 M NaCl, 3 mM ethylene diamine tetra acetic acid [EDTA], and 0.05% [v/v] surfactant P20, pH 7.4), Amine Coupling Kit, Human Fab Capture Kit, Human Fab Capture Kit, NTA Reagent Kit, Protein L, and Biotin Capture Kit were all obtained from GE Healthcare.

**CASE STUDY I: BINDING KINETICS OF OTHER RITUXIMAB BIOSIMILARS AND RISTOVA TO HUMAN FCRγIIIa (CD16A)**

The binding kinetics of Ristova, a rituximab biosimilar, and other rituximab biosimilars to human FcγRIIIa (CD16a) receptor (R&D systems)
Biosimilars were determined by SPR-based sensor system (GE Healthcare). Kinetic analysis of FcγRIIIa (CD16a) binding was performed by injecting different known concentrations of aggregates (from 0.25 to 4 μM) onto immobilized carboxymethyl dextran-coated CM5 sensor chips, which were used with His-coupling chemistry (13). All measurements were performed at 25 °C with a flow rate of 30 μL/min using HBS-EP buffer with association time 60 s followed by 60 s dissociation phase. KD were calculated from the sensorgrams using the 1:1 fit model using SPR-based sensor evaluation software (GE Healthcare) (Figure 2).

SPR was used to provide a comparison of the binding kinetics of rituximab biosimilars to human FcγRIIIa with respect to Ristova. As given in Table III, the KD value of Rituximab biosimilars to FcγRIIIa was calculated to be within the same order of magnitude as Ristova. KD values were compared, wherein Ristova exhibited higher binding affinity than the other rituximab biosimilars. Biosimilar two exhibited comparable affinity for binding to FcγRIIIa with respect to Ristova, but others yielded lower values.

**CASE STUDY: II BINDING KINETICS OF GCS-F BIOSIMILARS AND NEUPOGEN (FILGRASTIM) TO CD114-R**

The binding kinetic interactions of five different biosimilars samples of granulocyte-colony stimulating factor (GCSF) to human CD114-R receptor (R&D systems) was determined by Biacore X100 plus biosensor (GE Healthcare). For GCSF-R affinity analysis, CD114-R receptor was immobilized on a CM5 sensor chip surface according to the manufacturer’s recommendation with a level of ~200 response units (RU) reached. Samples were injected in a series of concentrations ranging from 2–32 nM (Figure 3) with association time 120s followed by 120s dissociation phase. All measurements were performed at 25 °C with a flow rate of 30 μL/min using HBS-EP buffer according to the manufacturer’s protocol. Kinetic constants were calculated from the sensorgrams using the 1:1 fit model using SPR-based sensor evaluation software (GE Healthcare) (Figure 3).

### Table III. The binding kinetics of different rituximab biosimilars and Ristova (rituximab) to FcγRIIIa were estimated by using SPR-based sensor system.

<table>
<thead>
<tr>
<th>Product</th>
<th>CD16a binding (SPR)</th>
<th>R max Value</th>
<th>U-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ristova</td>
<td>0.46</td>
<td>31.14</td>
<td>2</td>
</tr>
<tr>
<td>Biosimilar 1</td>
<td>0.13</td>
<td>39.09</td>
<td>2</td>
</tr>
<tr>
<td>Biosimilar 2</td>
<td>0.33</td>
<td>12.07</td>
<td>5</td>
</tr>
<tr>
<td>Biosimilar 3</td>
<td>0.10</td>
<td>40.4</td>
<td>5</td>
</tr>
<tr>
<td>Biosimilar 4</td>
<td>0.12</td>
<td>9.18</td>
<td>9</td>
</tr>
<tr>
<td>Biosimilar 5</td>
<td>0.17</td>
<td>27.75</td>
<td>2</td>
</tr>
</tbody>
</table>

### Table IV. The binding kinetics of granulocyte-colony stimulating factor biosimilars and Neupogen (filgrastim) to CD114-R were estimated by SPR-based sensor system.

<table>
<thead>
<tr>
<th>Product</th>
<th>CD114-R binding (SPR)</th>
<th>R max value</th>
<th>U-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neupogen</td>
<td>4.4</td>
<td>673</td>
<td>1</td>
</tr>
<tr>
<td>Biosimilar 1</td>
<td>2.79</td>
<td>503.3</td>
<td>2</td>
</tr>
<tr>
<td>Biosimilar 2</td>
<td>2.65</td>
<td>480.4</td>
<td>3</td>
</tr>
<tr>
<td>Biosimilar 3</td>
<td>1.73</td>
<td>475.5</td>
<td>4</td>
</tr>
<tr>
<td>Biosimilar 4</td>
<td>4.98</td>
<td>276.4</td>
<td>2</td>
</tr>
<tr>
<td>Biosimilar 5</td>
<td>4.37</td>
<td>256.8</td>
<td>1</td>
</tr>
</tbody>
</table>

**Figure 3.** Comparative analysis of granulocyte-colony stimulating factor biosimilars and Neupogen (filgrastim) for affinity to CD114-R by surface plasmon resonance. The color key (-4 μM, -2 μM, -1 μM, -0.5 μM, -0.25 μM) is same for all the sensorgram indicates known concentrations of analytes.
**Table IV** represents the KD value of GCSF biosimilars to CD114-R was calculated to be within the same order of magnitude as Neupogen. Biosimilar four exhibited little higher affinities than Neupogen for binding to CD114R, but others yielded lower values. Because nearly all mAb biosimilars are produced in mammalian cells, they exhibit different post translational modifications (PTMs), which results in heterogeneity. This could be attributed to differences in expression system, culture conditions, purification processes, formulations, or storage conditions of the product and need to be suitably addressed as per the “similar but not identical” paradigm.

**DATA ANALYSIS:**
**KEY OUTCOMES**
The equilibrium constant determines the ratio of the antibody association rate (kon) of the antibody, how quickly it binds to its antigen, and antibody dissociation rate (koff), how quickly it dissociates from its antigen. Chi² and residual values were used to evaluate the quality of fit between the experimental data and individual binding models. Plots of residuals indicate the difference between the experimental and reference data for each point in the fit. The Chi² value represents the sum of squared differences between the experimental data and reference data at each point. Lower Chi² values indicate a better fit; however, it is difficult to recommend absolute values for acceptance limits for Chi². U-value indicates the uniqueness value for the kinetic rate constants (19). Lower values indicate greater confidence in the results. Prior to analysis, sensograms are double referenced by first subtracting data from a reference flow cell and then subtracting a blank cycle where the buffer is injected instead of protein sample. Sensogram comparison requires that standards, controls, and samples have been generated in the same way using identical association and dissociation times (20, 21). The assay format must be the same, and it is not possible to mix multi-cycle kinetic data and single-cycle kinetic data in the same session.

**SPR provides a meaningful insight into the characterization of biotherapeutics and comparability of biosimilars present in the market.**

**CONCLUSION**
This review has demonstrated that SPR is a rapidly developing technique typically used for characterization of protein interactions and in screening for selection of antibodies or small molecules with preferred binding properties. In characterization, complete binding curves are normally fitted to defined interaction models to provide affinity and rate constants, whereas report points indicative of binding and stability of binding are often used for analysis of screening data. It is a high-throughput technique that can potentially serve as a useful tool to evaluate the higher-order structural integrity of proteins for characterization as well as comparability purposes. As an outcome of this review, SPR provides a meaningful insight into the characterization of biotherapeutics and comparability of biosimilars present in the market.

**ACKNOWLEDGEMENTS**
This work was funded by the Center of Excellence for Biopharmaceutical Technology grant under Department of Biotechnology, Government of India.

**REFERENCES**
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Process Validation Sets the Stage for Ongoing Manufacturing Quality

A properly designed validation program will detect variation and ensure control based on process risk.

CLIFFORD J. SACHS

Given the critical role that validated commercial manufacturing processes have over ensuring product performance, process validation is an essential product development activity for pharmaceutical and biotechnology organizations. Failure to develop appropriate and effective process validation can lead to substantial regulatory actions by regulatory agencies, which may include recalls, for cause audits, or even plant closures. To assist industry, FDA and the European Medicines Agency (EMA) have published guidance documents that define the general principles of process validation. This article provides a general overview of the requirements of process validation, as described in the process validation guidance documents issued January 2011 by FDA (1) and April 2016 by EMA (2), as well as a comparison of validation requirements for biologics products, which are covered by a biologics license application (BLA), with the validation requirements for small-molecule products, which are covered by a new drug application (NDA).

GENERAL REQUIREMENTS
The current good manufacturing practice (CGMP) regulations establish the need for process validation by requiring that drug products be produced with a high degree of assurance of meeting critical attributes, based on objective information and data obtained from laboratory-, pilot-, and/or commercial-scale studies. More specifically, the primary basis for process validation is provided in 21 Code of Federal Regulations (CFR) 211.100(a), which states the requirement for “written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess ...” (3).

The FDA guidance document provides the general principles and approaches that FDA considers appropriate elements of process validation for the manufacture of human and animal drug and biological products, including APIs or drug substances. Effective process validation as the guidance notes, contributes significantly to assuring drug quality and to meeting the following basic principles of quality assurance: quality, safety, and efficacy should be designed

CLIFFORD J. SACHS is managing consultant, Tunnell Life Sciences Consulting.
Ion-exchange chromatography (IEX) is commonly employed in the analysis of proteins to investigate charge heterogeneity. Particularly in the biopharmaceutical industry, IEX is routinely relied upon to characterize and monitor the charge variants of protein-based therapeutics such as monoclonal antibodies (mAbs), which can very often have implications on drug efficacy and accordingly be flagged as critical quality attributes. In some ways, there has been a paucity of analytical options for assaying charge heterogeneity. While both capillary electrophoresis and liquid chromatography (LC)-based separations with ion exchange stationary phases offer suitable means to gaining insights about charge variants, there has long been a need with both approaches to address resolution limitations and challenges related to method implementation and robustness.

In this webcast, we will describe:

- Principles and practices of IEX chromatography of proteins
- Challenges and concerns of mAb charge variant analysis
- IEX method development considerations for higher quality mAb analyses

**KEY LEARNING OBJECTIVES**

- Review the factors that affect protein IEX
- Understand the strengths and limitations of mAb analysis techniques
- Learn about developing high resolution LC- and LC/MS-based mAb analyses

**WHO SHOULD ATTEND:**

Biopharmaceutical scientists
- mAbs, ADCs in Drug Discovery and Development (not QC)
- Contract Research Organizations (CROs)
- Contract Manufacturing Organizations (CMOs)
- Universities/Research

**PRESENTERS**

Qi Wang, PhD
Senior Scientist, Chemistry R&D
Waters Corporation

Hua Yang, PhD
Principal Scientist, Scientific Operations
Waters Corporation

**MODERATOR**

Rita Peters
Editorial Director
BioPharm International

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**Presented by**

BioPharm International

For questions contact Kristen Moore at Kristen.Moore@ubm.com
or built into the product; quality cannot be assured only by in-process and finished-product inspection or testing; and each step of a manufacturing process must be controlled to assure that the finished product meets all quality attributes including specifications.

The FDA has defined process validation as “the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product” (1). The evidence comes from information and knowledge obtained during product and process development and must demonstrate that the commercial manufacturing process will consistently produce APIs and drug products that meet critical quality attributes. A properly designed validation program provides the means for detection of variation and an understanding of the sources and degree of variation; such a program will assure an appropriate level of control of the variation based on the degree of risk to the process and product, where the degree of control of attributes and parameters may be based on the risk to the process and process output. In addition, after the process is confirmed, continued verification activities must be performed to assure the process remains in a state of control when changes are made.

The EMA guidance document contains principles that are generally similar to the FDA guidance with a few notable differences. The EMA guidance specifies that retrospective validation is not acceptable, and that concurrent validation is only acceptable when there is a strong benefit-risk ratio to the patient; the FDA guidance allows for concurrent release of process performance qualification (PPQ), if described and justified in the PPQ protocol, but expects it will be used rarely. Another difference between the two documents is that the FDA guidance has a greater emphasis on the use of statistics. Also, the EMA guidance states that a minimum of three consecutive batches is generally considered acceptable, while the FDA guidance is less prescriptive and allows manufacturers to determine the number of batches needed to demonstrate that the process is sufficiently under control. Both guidance documents outline a lifecycle approach to process validation and emphasize that appropriate quality oversight is essential over the entire validation lifecycle.

### Table I: Process development and verification activities, FDA vs. European Medicines Agency.

<table>
<thead>
<tr>
<th>Stage</th>
<th>FDA</th>
<th>EMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Process design</td>
<td>Process characterization</td>
</tr>
<tr>
<td>2</td>
<td>Process qualification</td>
<td>Process development</td>
</tr>
<tr>
<td>3</td>
<td>Continued process verification</td>
<td>Process verification</td>
</tr>
</tbody>
</table>

**LIFECYCLE APPROACH TO PROCESS VALIDATION**

Throughout the product/process lifecycle, established quality attributes and parameters need to be evaluated for their impact on the process, product, and in-process material, and reevaluated as new information becomes available. The FDA and EMA guidance documents each introduced the lifecycle approach to process validation. While the specific validation stages are described using different terms, both documents establish that all attributes and parameters need to be evaluated for their impact on the process, product, and in-process material, and reevaluated as new information becomes available throughout the lifecycle, through the process development and verification activities listed in Table I.

In addition, both guidance documents encourage the use of modern pharmaceutical development concepts, quality risk management, and quality systems at all stages of the manufacturing process lifecycle. In particular, FDA guidance provides recommendations that reflect some of the goals of FDA’s initiative entitled “Pharmaceutical CGMPs for the 21st Century—A Risk-Based Approach,” especially with regard to the use of technological advances in pharmaceutical manufacturing, by encouraging the implementation of modern risk management and quality system tools and concepts. The EMA guidance also provides requirements for data to be included in commercial product regulatory submissions.

In Stage 1, process design (FDA) or process characterization (EMA), the objective is to obtain process knowledge and understanding as the basis for establishing an approach to process control for each unit operation and the process overall, including controls for examination of material quality and equipment monitoring. This stage consists of studies to capture and build on process knowledge, which may include early process development experiments, laboratory- or pilot-scale studies, design of experiment (DoE) studies, use of risk analysis tools and/or computer-based simulations, and establishing a strategy for process control by reducing input variability and through appropriate in-process monitoring and operational limits. Advanced strategies may include the use of process analytical technology (PAT) to adjust the processing conditions so that the output remains constant.

In Stage 2, process qualification (FDA) or process development (EMA), the objective is to evaluate the process design to determine whether it is capable of reproducible commercial manufacture. Process qualification (PQ) consists of two elements: design of the facility and qualification of the equipment and utilities; and process per-
formance qualification (PPQ), which combines the actual facility, utilities, qualified equipment, and trained personnel with the commercial manufacturing process, control procedures, and components. CGMP-compliant procedures must be followed, and qualification of equipment and utilities must be performed under quality unit-approved project plan(s) and formal protocol(s). Appropriate facility design must be in place, and commissioning and qualification activities must be completed prior to initiating PPQ. A successful PPQ confirms the process design and demonstrates that the commercial manufacturing process is performing as expected. Following successful completion of PPQ, acceptable, commercial-scale products manufactured during this stage may be released for commercial distribution.

In Stage 3, continued process verification (EMA), the objective is to provide continual assurance that the process remains in a validated state for commercial manufacturing, consistent with 21 CFR 211.180(e), which requires establishment of an on-going program to collect and analyze product and process data that relate to product quality. This is achieved by establishing a formal, quality unit-approved plan for performing on-going evaluation activities, which should include:

- A system to detect and characterize variability, detect unplanned departures from the process, and determine root cause
- Monitoring to assess and adjust process variability, as needed
- Collection of data to improve/optimize the manufacturing process
- Maintenance of facility and equipment.

The data collected should include relevant trending for process performance and for the quality of materials/components, in-process material, and finished products; the alert and action limits should be established. The data should be statistically trended and reviewed by trained personnel. The information collected should verify that the quality attributes are being appropriately controlled throughout the process. Continued monitoring and sampling of process parameters and quality attributes should be performed at the level established during the process qualification stage, until sufficient data are available to generate significant variability estimates. These estimates can provide the basis for establishing levels and frequency of routine sampling and monitoring for the particular product and process. Monitoring can then be adjusted to a statistically appropriate and representative level. Process variability needs to be periodically assessed and monitoring adjusted accordingly, both in real time and on an annual basis.

VALIDATION REQUIREMENTS FOR BIOLOGICS PRODUCTS

While the FDA guidance document provides general requirements that apply to both small-molecule and biologics products, the EMA guidance document provides specific points to consider for process validation of biologics with regard to the upstream process, the downstream process, and multi-facility production.

For the upstream process, the EMA guidance document provides detailed recommendations on process evaluation and verification activities for the cell culture steps. For the downstream process, the EMA guidance document provides detailed recommendations on process evaluation and verification activities for evaluating the capacity of purification procedures, establishment of adequate analytical methods, process conditions (e.g., column loading capacity, flow rate, column length), and performance parameters. Finally, for multi-facility production, the EMA guidance document provides detailed recommendations for re-evaluation of the process at a new site.

There is also a difference in the validation requirements for biologics products, which are covered by a BLA, with the validation requirements for small-molecule products, which are covered by an NDA. For an NDA, the PPQ must be successfully completed before commercial distribution of a drug product and facilities. In contrast, for a BLA, commercial-scale PPQ must be completed prior to the BLA submission. Also, while in both cases the facility must be ready for inspection at the time of submission, the PPQ data must be included in the BLA submission and facilities must be prepared to manufacture the complete product during pre-licensing inspection (21 CFR 601.4). To facilitate the inspection, manufacturers are expected to submit production schedules approximately two to four months after the BLA submission.

CONCLUSION

The process validation guidance documents provided by FDA and EMA provide the modern concepts of process validation. The guidance documents establish the lifecycle approach to process validation, encourage the incorporation of risk management principles throughout the product and process validation lifecycle, formally describe the process development activities to perform in order to establish the scientific basis for the process, and provide guidance for an ongoing evaluation of the process to ensure it remains in a state of control during routine commercial production.

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Prefilled syringes offer advantages to the manufacturer, caregiver, and patient. With fewer handling steps and ease of use compared with empty syringes, prefilled devices can help reduce medication errors. They do, however, pose challenges in manufacturing and require extensive testing.

Testing of empty syringes must be performed at the site where filling will be completed as part of incoming quality control efforts. And, filled syringes (combination of the syringe and drug product) must also be subjected to release testing.

Knowledge and understanding of the various tests involved is essential for ensuring patient safety. “The development of robust drug products based on prefilled syringes as primary containers requires an integrated holistic approach,” asserts Thomas Schoenknecht, head of R&D within the drug product services unit at Lonza Pharma & Biotech. “Aspects including formulation, process, packaging, device integration, analytics/quality control, and intimate knowledge of the user needs all must be taken into account,” he explains.

COMPLEX TESTING REQUIREMENTS
Similar to other sterile products, prefilled syringes must be sterile and free from pyrogens. In addition, according to Gregory Sacha, senior research scientist at Baxter BioPharma Solutions, they must be chemically, physically, and biologically stable with no change in performance over the intended storage and use time. In general, the regulatory requirements for testing prefilled syringes need to comply with the US and European pharmacopoeias, notes Nicolas Eon, global product manager for syriQ prefillable syringes at Schott Pharmaceutical Systems.

Testing must be compliant with existing test and release methods for empty containers and for containers filled with the drug product solution. As such, both drug and device regulations apply to prefilled syringes. The regulatory landscape for combination products is complex and product/country specific, according to Schoenknecht. In the United States, for example, several parts of 21 Code of Federal Regulations (1) (211

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cGMP for finished pharmaceuticals, 314 drugs, 600 biologics, and 800 devices) are applicable. There are separate requirements outlined in the European Union (EU) Medical Directives (2) and proposed revisions to EU GMP guidelines Annex 1 (3).

While International Organization for Standardization (ISO) standards are important instruments for harmonization, health authorities do not necessarily support or enforce them, but use them as a guidance for internal regulation development, according to Schoenknecht. “As an example, FDA guidance on GMP requirements for combination products (4) cites several ISO standards, such as ISO 11040,” he says.

In general, test methods are defined in ISO 11040-4, Part 4 (Glass barrels for injectables), Part 5 (Plunger stoppers for injectables), Part 6 (Plastic barrels for injectables), and Part 8 (Requirements and test methods for finished prefilled syringes). Other tests are outlined in ISO 80369 for small bore connectors for liquids and gases in healthcare applications: Part 1 (Small bore connectors) and Part 7 (Connectors for intravascular or hypodermic applications, which have replaced ISO 594-1 and -2), according to Eon.

For glass prefilled syringes for biologics, the requirements are based on technical report number 73 from the Parenteral Drug Association (5), Eon adds. With respect to inspection of prefilled syringes, ISO 2859 (Sampling procedures for inspection by attributes package) and ISO 3951 (Sampling procedures for inspection by variables) are applicable. “The PDA technical report comes from industry, with key users of prefilled syringes in the pharmaceutical community teaming up with the vendors of those containers to create a document that serves the industry as a white paper. It describes in broad detail what needs to be considered for the successful combination of a prefilled syringe with biologics and what enables combination with a drug-delivery device,” says Schoenknecht, who is one of the co-authors of the report.

**NUMEROUS OPPORTUNITIES FOR QC FAILURE**

Given that so many different tests must be conducted on empty syringes and syringes filled with product, it isn’t surprising that there are many opportunities for these complex systems to fail to meet quality requirements.

Cosmetic defects such as scratches are common. These units are rejected because it can be difficult to determine if a scratch is only at the surface of the material or if it is a crack. Insufficient container silicification can result in failure during break-loose and extrusion-force measurements and actual product use. For needle syringes, insufficient needle pull-out forces can occur due to weak needle assembly and imperfect adhesive polymerization control.

For filled syringes, failures depend on the drug product design (e.g., the formulation), the syringe process design, and the careful assessment of interplays, according to Schoenknecht. “One point of concern being controversially discussed as a major risk for product development is subvisible particles. However, failing subvisible particles requirements on stability is a negligible risk for most protein formulations containing polysorbate and given adequate particle characterization,” he observes. The presence of leachables and API impurities can be further challenges.

Other failures concern patient-related issues. “Patients can have difficulty using the combination product (user handling), and these issues should be considered as testing failures,” Schoenknecht says. High injection forces, long injection times, and general issues with gripping the syringe are examples.

**TESTING OF EMPTY STERILE SUB-ASSEMBLIES**

Testing empty syringes prior to filling presents a few challenges that largely relate to the fact that only one part of the combination product (sterile barrel) is being tested, according to Eon. “The impact of the drug product on the functionality of the syringe cannot be evaluated prior to filling, but testing is still needed to confirm the intended purpose for the combination drug product,” he explains.

Specific tests that should be performed on empty syringes include:

- Glide force testing to evaluate syringe lubrication (ISO 11040-4)
- Pull-off force testing of the tip cap or needle shield (ISO 11040-4)
- Flange break resistance testing (ISO 11040-4)
- Luer cone breakage resistance testing (ISO 11040-4)
- Needle penetration testing (ISO 11040-4, ISO 7864, ISO 9626, and DIN 13097-4);
- Needle pull-out force testing (ISO 11040-4)
- Luer lock adapter collar pull-off force testing (ISO 11040-4)
- Luer lock adapter collar torque resistance testing (ISO 11040-4)
- Luer lock rigid tip cap unscrewing torque testing (ISO 11040-4).

Retention volume and deliverable volume are also tested for prefilled syringes. The retained volume is important because it will affect the fill volume and filling tolerances during manufacturing, according to Sacha. This method can be challenging to implement, however, because variances in the values obtained during testing occur between analysts and are affected by how the tip cap is treated during the test.

“All of these tests give only information about the quality and perfor-
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mance of the container itself, though,” agrees Schoenknecht. “Final proof of a specific container closure system for a given drug product, consisting of the container with closures and liquid fill (drug formulation), suited to fulfill the requirements can be made using tests performed on the final combination product,” he asserts.

Schoenknecht also stresses that device development should be driven by human factor studies (user requirements) that lead to design input requirements. “Performance tests such as breakout- and extrusion-force measurements should be executed against the user requirements, which should take into account the capabilities of the intended patient population/group,” he explains.

FUNCTIONALITY TESTING
Functionality testing (e.g., gliding force, mechanical resistance, opening force, etc.) involves examination of the force required to initiate movement of the plunger and the pressure required to maintain the movement; the test is usually destructive. As a result, it is only performed with a reduced inspection plan (S-4) and limited sample population, which leads to a higher beta risk for the customer, according to Eon.

Carrying out these tests requires a clear understanding of the testing requirements listed in the cited ISO standard and the capability to implement and qualify the test methods in accordance to GMP standards, according to Schoenknecht. “Injection-force, break-loose force, and glide-force measurements can be particularly challenging because they depend closely on the inner diameter of needle, which can vary within tolerances,” he says.

CONTAINER CLOSURE INTEGRITY TESTING
“Sterility is the most important critical quality attribute of a parenteral/sterile drug product. Container closure integrity (CCI) testing (ISO 11040-4) is one of key tests to be performed to ensure the combination product is in full GMP compliance, guaranteeing sterility,” asserts Schoenknecht. CCI is required to ensure microbiological quality and thus sterility until point of use.

Lipid Nanoparticle Delivery Platform Demonstrates Improved Immune Response
A new vaccine approach for HIV has demonstrated improved immunogenicity against the p24 HIV protein by loading it and an immunostimulant agent onto nanostructured lipid carriers (NLCs).

Researchers conducted by Leti, a research institute of CEA Tech, and collaborators developed the approach using CEA-Leti’s Lipidots delivery platform (1).

The Lipidots nano-delivery platform encapsulates drugs in droplets of oil and delivers them to targeted cells. The 100-nm drops can enter the body’s lymphatic vessels and are carried to the lymph nodes where they trigger a stronger immune response.

When tested in mice and non-human primates, the approach enhanced immune responses against p24 by increasing specific antibody production and T-cell activation, when associated with Lipidots NLCs delivering the CpG immunostimulant. The lipid carriers protect the CpG nucleic acids from the extracellular environment and deliver it intracellularly into the dendritic cells, the researchers reported.

Micromotors Deliver Oral Vaccines
Scientists are exploring how magnesium particles could be used as tiny motors to deliver an oral vaccine against the bacterial pathogen Staphylococcus aureus to the mucus layer of the intestine (2).

Magnesium microparticles coated with titanium dioxide use water as fuel to generate hydrogen bubbles that power their propulsion. Researchers coated magnesium micromotors with red blood cell membranes that displayed the Staphylococcal α-toxin, along with a layer of chitosan to help them stick to the intestinal mucus. When given orally to mice, the micromotors safely passed through the stomach; an enteric coating then dissolved, activating the motors. Imaging showed that the micromotors accumulated in the intestinal wall much better than non-motorized particles.

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CCI testing evaluates the adequacy of container closure systems to maintain a sterile barrier against potential contaminants. Currently, regulatory guidance around CCI testing is ambiguous and provides limited details on how to properly assess CCI, according to Eon. He does note, however, that revisions to regulations (e.g., the new EU Annex 1) are being made to ensure a common understanding of expectations in relation to CCI testing.

Schoenknecht adds that the limitations of the individual technologies need to be understood and the most suitable methods selected and qualified for a given product. “The best solution is to have a holistic sterility/CCI strategy that follows a quality-by-design approach and comprises a phase-appropriate testing strategy,” he observes.

Issues with existing methods vary depending on the method. Some, such as dye-penetration testing, leak testing, and microbiological ingress testing, are destructive to the samples being tested. “These probabilistic methods also rely on a statistically representative number of samples from the batch and assume that any defect is uniformly present throughout the batch. All decisions are therefore made based on the small number of samples removed from the batch,” Sacha comments.

With others it can be difficult to demonstrate the sensitivity of the CCI test method, particular with respect to the positive control, according to Eon. Traditionally dye ingress, which is probabilistic, also has poor sensitivity, according to Schoenknecht.

Deterministic methods are non-destructive and can be used to test every unit from the batch. These methods include vacuum/pressure decay testing, high-voltage leak detection, and analysis of the head space within the syringe, according to Sacha. New technologies on the horizon for 100% CCI inspection based on x-ray imaging analysis or online leak testing are creating some excitement, according to Eon. The implementation of such online test methods might be extremely challenging and costly, though, according to Schoenknecht.

He points to an alternative approach that involves precise process validation of the filling process using the helium leakage method to ensure selected process parameters correlated to robust process performance. After much discussion within the industry, there seems to be consensus that the helium leak test method is one of the best methods for CCI. Lonza has developed proprietary CCI technology based on helium leakage testing in which prefilled syringes can be assessed in a very sensitive way, according to Schoenknecht. Helium gas leakage from samples is detected by mass spectrometry, with the ion counts proportional to the leak rate and thus quantifiable. The test can be used for vials, syringes, and other drug product formats at a range of temperatures, including with Lonza’s method down to -80 °C.

AUTOMATED INSPECTION FOR PREFILLED SYRINGES

Automatic inspection equipment is used to check the product for particles, for cosmetic defects, and for proper placement of the plunger, says Sacha. With automatic inspection, Eon notes, companies can enact 100% inspection instead of statistical process control (SPC), which is limited by the sample error. “Using 100% inspection ensures the lowest customer risk, enables parts per million quality level, and acts as a tool for process optimization and capability analysis,” he asserts.

Schoenknecht agrees that automatic control can ensure a 100% inspection of all syringes/containers per production batch following a robust reliable and reproducible testing process. “As such, a higher quality standard than for visually only inspected syringes can be reached by calculating performance data out of the data pool of syringes coming out of the glass converting process and following handling steps at the syringe vendor, helping to understand the robustness of the production process applied at the place of syringe production. However, inline CCI testing of the filled container usually has quite low sensitivity, and thus it is arguable if product quality is improved by using current CCI technologies on-line,” he observes.

It is important to note, though, that visual inspection of prefilled syringes is required under GMP. In addition, automated inspection instruments/methods need to be qualified/validated and the automated inspection system should perform as well as a human operator regarding failure detection rates, according to Schoenknecht. False-positive detection and creating too many false rejects can occur, and users of automatic inspection systems should be aware of the potential for such issues. He also notes that for smaller batches, such as for clinical studies, manual inspection is often preferred.

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**Drug Development — Contin. from page 19**

**BEST PRACTICES**

“The decision to pursue alternate drug delivery can occur at any stage of the drug discovery, development, or commercialization lifecycle,” states Rousset. “However, early awareness of potential benefits of alternative dosage forms and the pharmacokinetic parameters associated with the various routes of administration are key to shape robust development strategies.”

Additionally, there is a responsibility with the developer to engage and educate the relevant health agency about the latest cutting-edge technology. “It is best practice to gain clarity early by way of a pre-investigational new drug meeting, on the regulatory pathway, preclinical, clinical and any chemistry, manufacturing, and controls requirements that may be unique to the dosage form,” Rousset adds.

Some technological advances that Rousset specifies as being noteworthy include:

- Crystal engineering, as well as advances in polymer science, offer great promise in alternate dosage forms.
- Advanced top-down fabrication methods such as microfluidic synthesis and photolithography can enable more effective scale-up of nano-formulations
- Digital dispensing devices can pair uniquely with novel dosage forms, such as a roll dispenser with a continuous film that can be cut into desired sizes for personalized dosing and tracking of drug administration.

**PROMISING FUTURE**

In Huddleston’s opinion, the most promising dosage form for the future is that of parenteral forms for subcutaneous administration. “Parenteral dosage forms for subcutaneous administration are the most promising as they can provide an opportunity for therapies to be administered in the home setting,” he says. “Thus, subcutaneous delivery platforms with simple, patient-friendly designs will be the preferential dosage form in the future.”

Apart from subcutaneous administration, the local (topical) use of biologics, where systemic administrations and hence absorption are not relevant, offers potential as a ‘future sweet spot’ for Mahler. “Potential applications range broadly, such as in wounds, for wound healing, by inhalation to treat pulmonary diseases such as cystic fibrosis, or the potential use of biologics for local therapy of diseases such as Crohn’s disease,” he notes. “However, the in-vivo destabilization of biologics remains a key challenge for these topical administration routes.”

Additionally, he reiterates that the industry will continue to face challenges when attempting systemic administration via non-parenteral delivery for biologics as a result of molecular degradation in-vivo and the high cost of production. “These challenges may not be easily overcome without increasing patient safety risks,” he says. “Another approach that may be more worthwhile to focus efforts into is making parenteral products more attractive for patients and users, by decreasing potential pain sensations or related concerns, for example.”

According to Rousset, there are clear reasons as to why the majority of dosage forms on the market are oral, this dosage form is cost-effective, offers good stability, and is preferred by the patient due to the ease of administration. “Dosage forms such as oral thin films and orally disintegrating tablets are widely accepted and palatable, with the further potential benefits of circumventing first-pass metabolism and increasing drug onset,” she notes. “However, delivering proteins via the buccal or sublingual route remains a lofty goal in the field, but with advances in nanosized drug delivery systems and advanced manufacturing technologies, such applications may be realized in the not-so-distant future.”

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Strategic Ventures Reflect Dynamic Growth in China

Technology vendors are strengthening their positions in China as the nation emphasizes self-sufficiency in research, development, and manufacturing.

Agnes Shanley

Biopharmaceutical manufacturing figures prominently in China’s industrial plans. A growing population (the world’s largest), healthcare spending in the vicinity of US$ 4.6 trillion (roughly 6% of the nation’s gross domestic product), and strong support for innovation have resulted in growth that has surpassed previous predictions, according to Eric Langer, director of BioPlan Associates, which recently published its second edition of Advances in Biopharmaceutical Technology in China (1).

According to BioPlan, the Chinese biopharmaceuticals market exceeded $9 billion in 2018, most of it for monoclonal antibodies (mAbs). Of the 27 mAbs that have been approved in China, nine are already manufactured locally, and over 400 mAbs are now in development, Langer wrote in February 2019 and November 2018 in the Market Research Blog (2,3).

Currently, the country’s biopharmaceutical manufacturing base incorporates 180 biopharmaceutical manufacturing plants with more than 800,000 L of capacity, BioPlan research has found.

The country has 650 clinical trials underway for biologics. In 2015, the number of biologics patents filed, which had already begun to exceed US filings in 2011, was almost twice as large as the US figure, Langer wrote (3). WuXi Biologics, China’s largest contract research and contract development and manufacturing organization (CRO and CDMO) is building capacity in the United States and Singapore (4,5), but also plans to build a 1.6-million-ft² facility in Shanghai (6). Global technology vendors are strengthening their presence in China, as shown by some recent developments.

Local sourcing for single-use process equipment

During the last quarter of 2018, GE Healthcare and Wego Pharmaceuticals joined forces to provide a source of single-use consumable bioprocessing equipment in Weihai, China. The equipment is based on GE’s Fortem platform (7).

Integrated cradle-to-grave processing

Pall Corp., which established its first Center of Excellence in China in 2013, set up a Biotechnology Integrated Solutions Center of Excellence in Shanghai in December 2018. The center will offer consulting services, demonstrate technology, and provide testing and training (8).

Immunotherapies focus

In December 2018, Sartorius Stedim Biotech (SSB) began a partnership with China’s Immunochina Pharmaceuticals, a specialist in immunotherapies, that will provide it with preferred access to SSB’s platforms for development, scale-up, and manufacturing (9).

Mobius in China

In October 2018, Millipore Sigma revealed plans for its first single-use manufacturing facility in China. Using the company’s Mobius platform, the facility in Wuxi will provide both off-the-shelf and custom solutions (10).

Bioanalytical Equipment

Thermo Fisher Scientific opened its first analytical Bioprocess Design Center in Shanghai during the last quarter of 2018, part of its plan to establish a center of excellence in China. The 2700-m² facility offers access to bioprocess analytics equipment and to relevant expertise, with the goal of facilitating end-to-end bioprocess development (11).

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Also associated with this is a clear separation of duties when using a cloud provider. The cloud works in a similar way to a laboratory environment, where you have a separation of duties between the user collecting the data versus the person who is responsible for reviewing that the data are correct.

For a cloud environment, access to servers is restricted to only allow people who both have to interact with the hardware and do not know what is stored on the machines there. This provides a significant level of protection because it would take more than one person to perform an adverse event.

MOVING FROM AN ON-PREMISE ENVIRONMENT TO THE CLOUD

Moving to the cloud can pose several challenges for organizations moving from an on-premise deployment. These challenges mainly concern how the regulations are interpreted and what controls are put in place. For example, when deploying software on premise, it is possible to visually inspect the infrastructure, whereas this is not possible with the cloud—as providers rightly view access to their sites as a security risk.

While this could easily be interpreted as a limitation, these constraints can also be a benefit for software deployments where data integrity is paramount, as discussed previously. To support this, industry groups, such as PhUSE, have created cross-functional working groups to help break down barriers and make it easier for organizations to move their regulated deployments from on-premise to the cloud.

ASKING MORE OF THE CLOUD AND NEW TECHNOLOGIES

Organizations that have made the move to the cloud are now asking how it can provide even more benefits. Businesses are turning to emerging technologies such as machine learning and artificial intelligence to see if the data collected can be enhanced to gain more value and speed up the decision-making processes.

To successfully use machine-learning techniques, organizations need to produce large amounts of data. But as highlighted earlier, a large amount of data is one of the main reasons that organizations are moving to the cloud.

One area where machine learning has been successful is around image analysis, where the time it takes to analyze the image can be reduced alongside the additional benefit of accuracy being improved.

The question is, can machine learning help in other areas, such as the data review process performed by organizations or regulatory agencies? Could the time and accuracy of the process be further improved to get drugs to market faster?

FUTURE-PROOFING USING THE CLOUD

Historically, organizations with data management applications that capture good practice data for regulatory purposes have been responsible for the whole deployment. This included the provision of the infrastructure, the installation and configuration of the software, and confirmation that user requirements were met.

Today, the use of electronic data management systems is widespread and the move from using software on-premise to the cloud is gathering pace. These strategies can provide organizations with a number of efficiencies, even for those with the important task of managing regulated data.

In addition, the new technologies, such as machine learning, which can be accessed through the cloud, should be able to provide some further improvements around how data for regulated purposes can be captured, analyzed, and reported on.

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In recent times, several agencies and organizations have published regulations and guidelines on data integrity. It is hard enough keeping up with all the requirements and recommendations, and it seems that our processes and procedures are becoming ever more complicated because of these regulations. How can we prevent ‘death by complexity’?

Indeed, a lot has been published on the subject of data integrity (1–3), all with the best intentions, but not necessarily always providing the most practical of advice. Or, it may just be hidden in the vast amount of information provided in these documents. For example, a Pharmaceutical Inspection Co-operation Scheme (PIC/S) guidance document (2) states, ‘Examples of factors which can increase risk of data failure include complex, inconsistent processes with open ended and subjective outcomes. Simple tasks which are consistent, well defined, and objective lead to reduced risk.’ In 2016, the World Health Organization (WHO) (4) stated, ‘Good data process design should consider, for each step of the data process, ensuring and enhancing controls, whenever possible, so that each step is: consistent; objective, independent, and secure; simple and streamlined.’

Therefore, it is worth noting that simplification is a strong enabler of data integrity. So how does this work? There are some basic principles that should be applied consistently, such as:

- Simple, but clear and unambiguous instructions
- The sequence of instructions reflects the sequence of activities
- In a written document, the reader is never required to go back within the document
- Forms are logically laid out.

In one example, the records for the cleaning of a controlled area were scrutinized in an audit. According to the records, it was not clear when the operator cleaned a specific room and whether the cleaning was done correctly. The operator had to clean three rooms; this process was always done in a logical sequence, but that was not described in the instructions. As the operator was not allowed to take paper into these areas, the record was only completed once the operator had exited the area. The instructions were 45 pages long, which made it doubtful whether the operator could remember all the steps correctly.

Following the audit, the cleaning instructions for each room were extracted and written in a simple logical sequence. It was possible to fit the new sequence of instructions onto one or two pages (per room), which were laminated and thus be disinfected and permanently displayed in the respective areas. This way, the operator could consult the instructions whenever necessary. Furthermore, the cleaning logbook was redesigned to show on one line the date and time the operator entered the area, and the date and time the operation was complete, together with a field for any comments (rather than having each entry on a different line and often on different pages of the logbook).

This simple example illustrates that it is not always necessary to change the way operations are performed. What has to be done, however, is to break down instructions into manageable pieces, with tasks unambiguously described and presented sequentially. Why does this help with data integrity? Because it eliminates or prevents errors, reduces the risks of data omissions or errors, and enhances confidence in the system by inspectors.

In summary, though compliance with data integrity regulatory requirements may necessitate some more complex methodologies or systems, simplification of procedures and instructions is a key element of the compliance effort.
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