WuXi Biologics

Company Description
WuXi Biologics is a leading open-access technology platform contract services company. As a premier contract discovery, development, and manufacturing organization (CDMO), WuXi Biologics provides our worldwide clients with the necessary expertise, quality, and capacities to develop biologic drugs from concept to commercialization. Along with our WuXi AppTec affiliates, we provide the world with the one true, single-source approach. The efficiencies gained from this approach saves our clients critical time and money. Our company track record and achievements demonstrate our commitment to providing a truly one-stop service offering and value proposition to our global clients.

Markets Served
We support biologics drug developers of all sizes in all major markets, from top 20 pharmaceutical companies to virtual biotech companies by providing an integrated CMC package from concept to IND filing through to BLA and beyond. We also provide stand-alone services to overcome the challenges at a particular stage of development. Our expertise covers all facets of development for various types of biologics, including monoclonal and bispecific antibodies, recombinant and fusion proteins, and antibody drug conjugates.

Services and Capabilities
Occupying more than 1,000,000 sq. ft. of lab and manufacturing space, our network of facilities operates under global regulatory standards and provides our clients unparalleled capacities across the discovery, development, and manufacturing continuum. We offer GMP clinical and commercial manufacture of Drug Substance and Drug Product in multiple sites including the world’s largest mammalian cell culture GMP facility using disposable bioreactors. All the facilities are located within 1–2 hours’ drive from each other and provide a simplified supply chain for our global clients.

WuXi Biologics offers open-access technology platforms and a unique single-source discovery, development, manufacturing, and testing service for protein-based therapeutics.

Our comprehensive one-stop offerings include:
• Antibody discovery
• Custom small-scale, research-grade protein generation
• Cell line development
• GMP cell bank manufacture/characterization
• Assay development, qualification, and validation
• Bioconjugation development
• Cell culture process development
• Purification process development
• Formulation development
• Protein characterization
• Drug substance manufacture
• Drug product formulation and fill
• Biosafety testing (e.g., viral clearance)
• GMP lot release testing
• Stability studies
• Worldwide regulatory submission support.
BioPharm International integrates the science and business of biopharmaceutical research, development, and manufacturing. We provide practical, peer-reviewed technical solutions to enable biopharmaceutical professionals to perform their jobs more effectively.

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From the Editor

Wanted: A Highly Skilled Biopharma Workforce

Each year, BioPharm International conducts a survey of the biopharma employment environment to assess trends, patterns in salaries and benefits, and employee satisfaction with careers in the industry.

In addition to the compiled statistics from the 2017 survey (1) reported in this issue (2), the survey gathers participant commentary on employment-related topics. As expected, when you ask people for anonymous feedback about their work, the answers range from amusing to angry to thoughtful. Most important, the comments provide honest feedback about a deeply personal topic: the employee’s chosen profession, source of income, and the contributions they make to a cause. Recurring themes in the comments included:

- In cost-cutting measures, biopharma companies are moving research functions offshore.
- The competitiveness of the job market depends on geographic location.
- In competitive areas, it is very difficult to find and retain qualified talent.
- Technology advances in the biopharma sector will change employment in ways not seen in the traditional pharma sector.

The need for adequate staffing, skilled personnel, and training was another common theme. Respondents cited a need for training in leadership and management skills, regulatory science and affairs, technical management, analytical techniques, and advanced technology skills.

Limited availability of qualified workers can have a negative effect on bio/pharma industry growth. Eric Langer noted that employment concerns are one roadblock to continuing growth for the biopharmaceutical industry (3). More than one-half of bioprocessing facilities experienced capacity problems in 2017 due to difficulties in hiring needed operations staff. Outsourcing manufacturing processes due to staff limitations may not be a solution, he noted, as contract manufacturers also face hiring problems.

Up to the job?

In the 2017 survey, less than 4% of the respondents said new hires were “extremely” well trained for their job functions. Three-quarters of the respondents ranked new hires as “adequately trained, but not exceptional,” and more than 18% said the new hires were poorly trained, “I don’t understand how they got their jobs.”

More than 65% of the respondents expressed some dissatisfaction with the lack of training and continuing education at their organization. More than 22% said the company did not provide adequate training for basic skills; 43% said the company did not provide advanced training for employee professional growth.

Drug companies need highly skilled, knowledgeable scientists, engineers, technicians, and professionals to develop and manufacture new therapies. Bringing a new drug to market is a long-time, high-investment endeavor. Demands for financial performance, however, have short-term horizons.

Both employers and employees need to address the training questions. What are the responsibilities of employees to develop their own workplace skills? Will their personal investment in training and education result in career or salary advances? Are biopharma companies willing to invest in training? Will that training be sufficient to provide for the skilled workforce needed to get the job done?

References

The Parenteral Drug Association (PDA) is the leading global provider of science, technology, regulatory information, and education for the pharmaceutical and biopharmaceutical community. For more than 70 years, since its founding as a non-profit in 1946, PDA has been committed to developing scientifically sound, practical technical information and resources to advance science and regulation through the expertise of our more than 10,300 members worldwide.

Recognized for our expertise and authority in the field of parenteral science and technology, PDA is leading the way in promoting the exchange of information on rapidly evolving technology and regulations to ensure high-quality pharmaceutical production.

PDA supports its mission to advance pharmaceutical and biopharmaceutical science and regulation so members can better serve patients by:

- Promoting advances in pharmaceutical and biopharmaceutical science
- Providing global forums for the scientific community, regulators, and industry professionals on emerging trends within the industry
- Facilitating development, testing, and qualification of new technologies
- Delivering unique, hands-on education and training through PDA’s manufacturing training facility
- Fostering career-long learning and professional development
- Encouraging scientific information sharing among industry peers
- Continuing to be a leading and influential contributor of information and expertise for the global regulatory and harmonization process.

PDA draws its strength from its members, which includes a corps of 2,500 active volunteers. Our conferences, meetings, and courses bring together pharmaceutical manufacturers, suppliers, end users, academics, and regulatory officials for an unprecedented level of exchange on timely issues of mutual interest and concern.

Through the development of Technical Reports on pressing industry topics and responses to regulatory initiatives, PDA and its members influence the future course of pharmaceutical products technology. Our internationally recognized publications, *PDA Journal of Pharmaceutical Science and Technology* and *PDA Letter*, keep pharmaceutical manufacturing professionals up to date on the latest science and current industry and regulatory news.

Together, these activities promote the advancement of pharmaceutical science in the interest of the ultimate end-user—the patient.

**PDA—Connecting People, Science, and Regulation**

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**NUMBER OF EMPLOYEES**
45

**YEAR FOUNDED**
1946
2018 PDA Annual Meeting

Agile Manufacturing Strategies: Driving Change to Meet Evolving Needs

The 2018 Annual Meeting will address industry “hot topics,” including the end users’ patient perspective, innovative manufacturing strategies, disruptive technologies, and product value chain logistics. Attend to find out about the latest trends in Big Data, Artificial Intelligence, and robotics!

NEW FORMAT FOR 2018:
Same high-quality content in an ALL NEW meeting format!

In response to attendee feedback, PDA is debuting a NEW meeting format at the 2018 PDA Annual Meeting, designed to better meet the needs of attendees.

Please note these important changes to the 2018 PDA Annual Meeting Schedule:

• The Conference will now begin with the Opening Plenary at 1:00 p.m. on Monday, March 19
• The Grand Opening Celebration will kick off in the Exhibit Hall at 5:00 p.m. on Monday, March 19 – take advantage of your first opportunity to see the latest products and services and meet with exhibitors!
• Interest Group sessions will be held at the same time as the breakout sessions, giving attendees more sessions from which to choose during the day and allowing for more free time in the evening
• The Closing Reception will take place on Wednesday, March 21 at 7:00 p.m. – Be sure to stay and celebrate with us!

Discover how the industry is using novel approaches to stay agile in the face of development and commercialization of innovative therapies. Sessions will focus on exciting topics such as continuous biomanufacturing, serialization, advances in analytical sciences and quality control strategies, patient-centered precision medicine, and next-generation manufacturing.

Don’t miss the Exhibit Hall where vendors and suppliers will showcase their latest technologies and offer solutions to current and future pharmaceutical manufacturing challenges.

Be a part of one of the most exciting events of 2018!

Learn more and register at pda.org/2018Annual

Immediately following the Annual Meeting, from March 21-22, 2018, the 2018 PDA Manufacturing Intelligence Workshop will explore how the industry is developing its capacity to advance the use of big data in manufacturing and supply chain management.

Learn more and register at pda.org/2018MI

And, on March 22-23, 2018, PDA Education will host a choice of seven courses as part of the 2018 PDA Annual Meeting Course Series to help you further advance your knowledge.

Learn more and register at pda.org/2018AnnualCourses
Advances in biomedical science transformed medicine in 2017, as seen in FDA approval of the first gene therapy that modifies human cells to treat and possibly cure a deadly disorder. Recent months have witnessed the emergence of truly breakthrough therapies, led by Novartis’ CAR-T therapy Kymriah (tisagenlecleucel) for patients with relapsed acute lymphoblastic leukemia; this approval was followed by Yescarta (axicabtagene ciloleucel) from Gilead Sciences and Kite Pharma for broader treatment of a similar lethal condition. Spark Therapeutics’ Luxturna (voretigene neparvovec) promises to cure a rare genetic eye disorder that causes blindness. FDA reports that some 40 companies are developing CAR-T technologies for multiple indications and that it is monitoring more than 600 active investigational new drug applications (INDs) related to gene and cellular therapies.

Biopharma researchers also are achieving success in developing oligonucleotide therapies, including antisense drugs and short interfering RNA treatments (siRNAs) that can modulate immune pathways. Safety issues derailed advances in this area some 20 years ago, but now better understanding of oligo chemistry and product characterization are driving research programs. FDA set the pace in approving Biogen’s Spinraza (nusinersen) in December 2016, a first treatment for spinal muscular atrophy, which is often fatal for infants. More controversial was FDA’s approval of Sarepta Therapeutics’ Exondys 51 (eteplirsen) to treat Duchenne muscular dystrophy, due to its reliance on an uncertain surrogate endpoint to demonstrate efficacy.

Scientific advances in genome editing technology, such as CRISPR-Cas9, also expand possibilities for using gene editing techniques to correct disease-causing mutations. While systems that edit DNA are hard to reverse, changes from RNA-editing procedures disappear over time, which can be a plus, or a liability, depending on the situation. Although the long-term effects of these drugs are unknown, these initial successes have spurred optimism about further development of treatments for both rare and more prevalent serious conditions, particularly neurological diseases such as ALS, Alzheimer’s disease, and Huntington’s disease.

CMC CHALLENGES
Better understanding of manufacturing, formulation, and pharmacology of these emerging products is important in advancing development beyond early testing stages. At a conference in October 2017 on oligonucleotide-based therapeutics sponsored by FDA and the Drug Information Association (DIA), experts explored strategies for tackling quality risk management, setting specifications, and assuring compliance with chemistry, manufacturing, and control (CMC) standards for experimental treatments. Presentations covered the importance of control strategies and the need to characterize and qualify impurities, including the use of platform data in assessing oligo impurities.

Firoz Antia, director of technical development at Biogen, described the complexities of addressing CMC issues in developing Spinraza, citing challenges in establishing impurity controls for starting materials, achieving process consistency, and classifying critical vs. non-critical limits. Specifications for clinical batches had to be negotiated, along with strategies for gaining waivers from in-country testing requirements for limited clinical supplies. FDA approved Spinraza with a number of post-approval study and quality assessment commitments, including programs to
re-evaluate drug substance method validation data and acceptance criteria, to re-examine impurity acceptance criteria based on data from commercial batches, and to conduct stability testing on drug product process validation batches. The company also may find it appropriate to tighten specification limits and may explore room temperature storage possibilities and a continuous manufacturing system for future production.

These challenges were echoed by Vidhya Gopalakrishnan, senior vice-president at Quark Pharmaceuticals, which has several oligo compounds in clinical trials. Development involves controlling for impurities in clinical supplies and establishing CMC strategies for global product development, he observed. And process scale-up further requires identification and qualification of thresholds and specifications.

**COMBOS CRUCIAL**

The process of developing and delivering cutting-edge gene therapies also involves ensuring reliable and accurate delivery and dosing for patients, objectives that increasingly involve devising combination products that utilize prefilled syringes and autoinjectors for safe and accurate patient treatments. Biopharma manufacturers thus face additional challenges in working with device makers to devise, test, and produce reliable and efficient combination products, commented Bret Coldren, director of pharmaceutical development at Ionis Pharmaceuticals at the oligo conference. He emphasized the importance of establishing and evaluating device design controls early in drug development and of ensuring compatibility of the components, as drug viscosity may affect syringe design, and inhalation devices need to efficiently target a lung treatment.

Provisions in the 21st Century Cures Act and in the FDA Reauthorization Act (FDARA) approved in August 2017 bolster FDA’s Office of Combination Products (OCP) and its role in advising on whether a new combination therapy should be designated as a drug, biologic, or device, key to determining which FDA center serves as the regulatory lead. OCP officials and other FDA staffers outlined the latest developments in this area at a DIA conference on combination products, also in October in Bethesda, MD, highlighting efforts to update existing guidances and to prepare additional advisories on labeling issues and bridging studies.

A main OCP initiative is to provide more assistance to manufacturers, particularly those developing more complex cellular and gene therapies that seek to utilize auto injectors, metered dose inhalers, and nasal sprays. OCP receives hundreds of inquiries on issues related to product classification, many seeking early advice on the regulatory designation process. FDA officials emphasize the importance of achieving consistency throughout the agency in making timely decisions on combination product oversight to support the development and approval of innovative drug delivery approaches.


Another key issue for combination products is to understand and comply with human factor study requirements. Guynh Nhu Nguyes, associate director for human factors in the Division of Medication Error Prevention and Analysis in the Center for Drug Evaluation and Research (CDER), outlined at the oligonucleotides conference how human factors testing can ensure appropriate dosing and drug delivery and avoid medication errors and patient harm. FDA published a draft guidance in February 2016 on human factors studies for combination products (2) and is reviewing comments to finalize the policy.

As FDA and industry continue to scope out regulatory pathways to bring critical new therapies to patients, they will be looking for strategies to address the high cost of gene and other breakthrough products that threaten to limit patient access to treatment. Current processes for developing and delivering complex new drugs are expensive and contribute to higher prices for these vital therapies. The situation puts a premium on efforts by FDA and biopharma companies to identify efficiencies and improved methods for testing and producing cutting-edge medical technologies. It also highlights the importance of strategies that encourage coverage and reimbursement for life-saving therapies by both public and private payers.

**REFERENCES**


Wyatt Technology Corp.

COMPANY DESCRIPTION
Wyatt Technology, a 35-year old family-owned and operated enterprise, is the world’s largest company dedicated to SEC–MALS detectors for absolute macromolecular characterization. Our instrumentation provides the essential techniques for characterizing macromolecules and nanoparticles in solution, in order to determine molar mass, size, charge, and interactions. Wyatt’s extensive applications laboratories and its full-time staff (including more than 20 PhD scientists) means our customers receive deep technical expertise and support. To ensure the personal touch, “Light Scattering University” (LSU) is included with most of our instruments. We bring you to Santa Barbara to de-mystify light scattering, work you hard but feed you well, and, of course, explain how to get the most from your Wyatt Technology equipment.

Main Chromatographic Techniques Supported
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• GPC/SEC/GFC
• RPC
• Field-flow fractionation

Markets Served
Wyatt’s products are the most widely used multi-angle lightscattering (MALS) detectors in the world. They are employed in thousands of laboratories including, but not limited to, companies involved in biotechnology, pharmaceutical development, chemical, and petrochemical research, in addition to government national labs and academic facilities.

Major Products/Services
WTC’s family of instruments includes:
• DAWN HELEOS: An 18-angle SEC–MALS detector that can be used at ambient, elevated, and below ambient temperatures for polymers, particles, and biopolymers.
• miniDAWN: A SEC–MALS detector ideal for proteins and peptides and molar mass materials below 1 million Da.
• μDAWN: The world’s first MALS detector for UHPLC. Compatible with all UHPLCs for molar mass and size determinations.
• UT-rEX: The world’s first refractive index (RI) detector for UHPLC. Operates at the same wavelength of light as the μDAWN.
• Eclipse system: For separation of macromolecules and nano particles in solution.
• Optilab TrEX: The most advanced RI detector in the world with 256 times the detection power and 50 times the dynamic range of any other RI detector. The TrEX can be operated below or above ambient temperature and determine dn/dc at the same wavelength of light as the lightscattering instrument.
• WyattQELS: A quasi-elastic (dynamic) lightscattering instrument that can be interfaced to the DAWN HELEOS or the miniDAWN TREOS to determine particle sizes as small as 1 nm.
• ViscoStar viscometer: A state-of-the-art intrinsic viscosity detector that can be operated above or below ambient temperature with its precise Peltier thermostatic controls.
• WTC Protein Columns: A family of new silica based columns specifically designed for SEC–MALS protein applications. These columns retain all the important features of a first-class SEC column for protein separations.

Facility
WTC maintains more than 55,000 ft² of modern electronics, optical prototype, machine shop, and laboratory facilities in Santa Barbara, California.
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- Analyzing 1,536 samples
- All of the above

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Outsourcing in the biopharmaceutical industry had a productive 2017. A flurry of acquisitions, an expansion of biotechnology needs, and a growth in new facilities and services offered were seen. According to Eric Langer of BioPlan Associates, Inc., this growth may be due to commercialization, which would increase the need for biopharma outsourcing.

“There have been recent successes in gene and cell therapy, where the next stage in commercialization or even expanded clinical development [is] likely going to need the expertise available from those service providers offering these highly technical, and relatively rare, development and manufacturing services. This may be the first time in our industry where the hurdles to commercialization will not be so much technical as staffing/operational. Without these talented hands, there may be a real bottleneck as some of these novel therapies move through the clinic toward commercial success,” says Langer.

The following are some of the highlights from the 2017 year in biopharma outsourcing.

**INDUSTRY MILESTONES**

FUJIFILM Diosynth Biotechnologies completed its 100th program using pAVEway Advanced Protein Expression system in June 2017. pAVEway was developed by FUJIFILM Diosynth Biotechnologies to enable the reliable and scalable GMP manufacturing of *E. coli*-based processes. The pAVEway system has the ability to control protein expression by allowing expression and secretion to be coupled (1).

MilliporeSigma, the life-science subsidiary of Merck KGaA, made advances in CRISPR technology in 2017. In May, MilliporeSigma announced that it had developed an alternative CRISPR genome-editing method called proxy-CRISPR. The company’s proxy-CRISPR technique can cut previously unreachable cell locations, making CRISPR more efficient, flexible, and specific, and giving researchers more experimental options. With MilliporeSigma’s CRISPR genomic integration technology, scientists can replace a disease-associated mutation with a beneficial or functional sequence, a method important for creation of disease models and gene therapy (2).

In June 2017, MilliporeSigma was granted patent rights relating to the use of CRISPR in a genomic integration method for eukaryotic cells, by the Australian Patent Office (3).

**MERGERS AND ACQUISITIONS**

In January 2017, WuXi AppTec announced the acquisition of the biology-focused preclinical drug discovery contract research organization (CRO), HD Biosciences (HDB). HDB is headquartered in Shanghai and has operating facilities in Beijing and San Diego, CA. HDB offers plate-based pharmacology and screening capabilities, hit identification, lead discovery, and in vivo pharmacology (4).

In April, Sartorius Stedim Biotech (SSB) acquired Umetrics, a specialized provider of data analytics software for development and manufacturing processes headquartered in Malmö, Sweden. SSB has been a cooperation partner of Umetrics since the end of 2012, distributing and co-marketing their software to players in the biopharmaceutical industry. Umetrics’ software has applications in critical process steps of biopharmaceutical manufacture and development (5).

On June 14, 2017, JSR Life Sciences announced that it agreed to acquire Selexis SA, which specializes in mammalian cell-line generation. This will mark the second major biotechnology addition to the company, following JSR Corporation’s acquisition of KBI Biopharma in 2015 (6).

Thermo Fisher Scientific completed its acquisition of Patheon, a contract development and manufacturing organization (CDMO) serving the pharmaceutical and biotechnology sectors in August 2017. Patheon will become part of Thermo Fisher’s laboratory products and services segment (7).
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EACH ISSUE INCLUDES:
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- Upstream Processing
- Downstream Processing
- Peer Reviewed Technical Notes
- Product Spotlight
- Perspectives on Outsourcing

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In August 2017, MilliporeSigma announced an agreement to acquire Natrix Separations, an Ontario, Canada-based provider of hydrogel membrane products for single-use chromatography. This move is part of MilliporeSigma’s efforts to drive next-generation bioprocessing (8).

In September 2017, Eurofins Scientific acquired EAG Labs, which it later rebranded as EAG Laboratories, to expand its reach in North America (9).

Catalent acquired Cook Pharmica, a Bloomington, Indiana-based biologics contract development and manufacturing organization, in October. The acquisition strengthens Catalent’s position in biologics development and analytical services, manufacturing, and finished product supply (10).

In October 2017, Lonza acquired a clinical-stage mammalian manufacturing facility in Hayward, CA from Shire. Assets include 1000-L and 2000-L single-use bioreactors and associated downstream capabilities (11).

**NEW FACILITIES**

EAG Laboratories announced on April 25, 2017 that the company is expanding a dedicated cell biosay laboratory in Columbia, MO, tripling the footprint of its existing facility. The expansion includes cell-culturing incubators and new instrumentation to increase capacity and assay throughput (15).

In August, Cambrex announced the expansion of its High Point, NC facility with a 11,000-ft² analytical laboratory. The expansion includes high-performance liquid chromatography, mass spectrometers, and support equipment (16).

In September 2017, MilliporeSigma opened its first end-to-end biodevelopment center in Shanghai, China. The center will provide a range of process development capabilities and services, including upstream and downstream process development, non-GMP clinical production, and cell line development (17).

**REFERENCES**

THE DIFFERENCE OF A
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Complex biologic drugs, including personalized medicines, demand more sophisticated formulation and manufacturing methods, as well as talented, experienced pharmaceutical scientists and engineers to deliver therapies to patients. Advanced technology for manufacturing is expected to increase the required skill sets of biopharma workers.

These factors suggest a challenge for biopharma employers and a positive employment picture for biopharma employees. Consider the active mergers and acquisitions nature of the biopharma sector, financial pressures from shareholders and payers, and pressure to reduce costs, however, and the end result may be conflict between employer priorities and employee career paths.

Respondents to BioPharm International’s annual employment survey (1) shared opinions about the current employment environment, expressed reservations about compensation and workloads, and indicated that better career opportunities were a top priority. While respondents working in the biologics-based drug sector generally agreed with their counterparts in the broader pharmaceutical market (2), there were some differences.

Respondents reported mixed opinions about business performance. More than 45.3% reported that business increased in 2017 compared to 2016 (3). The number reporting a drop in business activity rose slightly, and the number of companies hiring new workers dropped slightly.

Contin. on page 19
Please rate your satisfaction with your current salary.

| I am paid below market value, considering my level of expertise and responsibility. | 23.5% | 21.7% |
| I am paid within market value for my job function, but at the low end of the range, considering my level of expertise and responsibility. | 36.4% | 38.6% |
| I am paid fairly for my level of expertise and responsibility. | 37.0% | 38.2% |
| I am paid excessively for my level of expertise and responsibility. | 3.1% | 1.5% |
Bio/pharma workers contemplate job and career changes.

- **I would like to leave my job, given the opportunity.**
  - Strongly Agree: 10.0%
  - Somewhat Agree: 24.0%
  - Somewhat Disagree: 22.7%
  - Strongly Disagree: 35.3%

- **I do not expect to leave my job in the coming year.**
  - Strongly Agree: 14.8%
  - Somewhat Agree: 34.8%
  - Somewhat Disagree: 27.5%
  - Strongly Disagree: 14.9%

- **I would like to change careers and leave the bio/pharma industry.**
  - Strongly Agree: 0.4%
  - Somewhat Agree: 19.5%
  - Somewhat Disagree: 40.9%
  - Strongly Disagree: 39.2%

**In your career, how long, on average, have you stayed with the same employer?**

- Less than 2 years: 15.3%
- 3 to 5 years: 18.2%
- 6 to 10 years: 27.1%
- 11 to 20 years: 30.8%
- More than 20 years: 6.8%

**If it were necessary for you to change jobs this year, how would you assess the job market?**

<table>
<thead>
<tr>
<th>2017</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>17.1%</td>
<td>27.1%</td>
</tr>
<tr>
<td>46.4%</td>
<td>39.6%</td>
</tr>
<tr>
<td>22.1%</td>
<td>17.1%</td>
</tr>
<tr>
<td>14.3%</td>
<td>16.3%</td>
</tr>
</tbody>
</table>

**My company provides adequate training for basic jobs skills.**

- Strongly Agree: 22.5%
- Agree: 21.0%
- Disagree: 50.5%

**My company provides advanced training for employee professional growth.**

- Strongly Agree: 48.5%
- Agree: 15.2%
- Disagree: 31.3%

Due to rounding, some percentages may not add up to 100%. Some questions allowed multiple answers. Results based on 2017 BioPharm International employment survey.

1970 Employment Survey

BioPharm International www.biopharminternational.com December 2017
2017 Employment Survey
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from 27.5% in 2016 to 25% in 2017. The number of respondents who felt “more secure” in their positions in 2017 rose to 22.6% versus 18.6% in 2016 (2); however, more respondents said they felt less secure in 2017 (33.6%) compared with 25.4% in 2016.

Opinions about the job market also varied. While 40.5% of the biologics-market respondents said the job market was moderately competitive (compared to 44.3% for the entire pharma audience), 24.1% of the biologics group (vs. 25% for global audience) said the market for jobs was competitive; there are more qualified candidates than open jobs. The remaining 35.4% said there are few qualified applicants for open positions and employers must compete for qualified candidates.

SURVEY RESPONDENT PROFILE
The survey, fielded in September and October 2017, drew more than 180 responses from the United States (70%), Europe (18.6%), Asia (5.8%), and other regions. Respondents primarily were full-time, permanent employees (87.1% of respondents) at innovator biopharmaceutical companies (44.1%), generic-drug manufacturing companies (34.1%), contract research and manufacturing organizations (15.8%), and consulting firms (6.4%).

The respondents represented companies that develop or manufacture large-molecule drugs, vaccines, and cell therapy or regenerative medicines; more than half reported that their companies are also involved in small-molecule drug development, an indicator of the adoption of biologic drug development at more traditional pharma companies. The respondents worked at privately held companies (44.1%), publicly traded companies (34.1%), and non-profit/academic/government groups (17.7%).

Respondents in the biologics sector tended to work for smaller companies compared with the respondents in the broader pharma market. More than 36% work for companies with more than 5000 employees (vs. 42.2% for the entire pharma market). More than 40% work for companies with fewer than 500 employees, vs. 34.4% for the broader pharma market.

The respondents were evenly split in tenure in the biopharma industry; 29.3% had fewer than 10 years of experience, 31.7% had 10–20 years, 30% had 20–35 years of experience, and 9% have worked in the industry for more than 35 years. About one-half of the respondents worked outside the bio/pharma industry for more than five years. More biologics-based workers held doctorate-level degrees or higher (41.2%) compared with the broader market (34.2%).

A LOT MORE WORK, A LITTLE MORE PAY
The survey indicates that biologics-based employees work more hours than counterparts in the broader pharma market. Workloads increased significantly in 2017, with 65% reporting increases compared with more than 51.3% in 2016. Nearly 40% of the respondents said they worked more hours in 2017 than two years ago, up significantly from 31.1% in 2016.

While 61% of the respondents said they were contracted to work approximately 40 hours per week, only 23.7% reported working 40 hours. Nearly 30% said they were contracted for more than 40 hours per week; however, 70% of the respondents said they work 40 or more hours per week.

Respondents reported similar paid vacation time in 2017 compared with 2016; 48.7% were eligible for four or more weeks of paid vacation; 31.6% reported that they used their full allotment of vacation, personal, and sick time, up slightly compared to 2016. One-quarter of the respondents said they used less than half of the available time off.

Salaries were up slightly; 61.1% reported a salary increase in 2017, up from 58.5% in 2016.

Satisfaction with salary levels were similar to the past two years; more people in the biologics sector were dissatisfied with their compensation levels, in comparison to the broader pharma market. Nearly 60% were dissatisfied with their compensation; 36.4% of the respondents said they were paid at the low end of the salary range for their job function for their expertise and responsibility; 23.5% said they were paid below market value.

CURRENT JOB, OR LONG-TERM CAREER
While three-quarters of the respondents have more than 10 years of experience in bio/pharma, 9% said they stayed with the same employer—on average—for less than two years; 27.1% stayed for three to five years. Less than one-third of the 2017 respondents said they stayed with an employer for an average of 6–10 years; 33.5% stayed with the same employer for more than 10 years.

In addition to salary and benefits, employee recognition can play a role in job satisfaction. Similar to the global audience responses, most respondents said their work is fully valued by their employer (30% strongly agreed; 42% agreed). More than 82% of respondents said their skills and training are used to the fullest level. Only 52% see opportunity for career advancement in their current position; 63% reported opportunities for professional advancement at their current companies.

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Eppendorf AG

Eppendorf is a leading life-science company that develops and sells instruments, consumables, and services for liquid, sample, and cell handling in laboratories worldwide. Its product range includes pipettes and automated pipetting systems, dispensers, centrifuges, mixers, spectrometers, and DNA amplification equipment as well as ultra-low temperature freezers, fermentors, bioreactors, CO₂ incubators, shakers, and cell manipulation systems. Consumables such as pipette tips, test tubes, microtiter plates, and single-use bioreactor vessels complement the range of highest-quality premium products.

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Much of the commercial production of biologic therapeutics is based on the use of recombinant cell lines, and product quality is verified through testing. This testing approach typically depends on fixed process conditions and extensive testing of the end product (1). However, using a quality-by-design (QbD) approach that employs predictive modeling can improve the quality of end product as well as the efficiency of the bioprocess.

REAL-TIME QUALITY CONTROL
Integrating process analytical technology (PAT) into the bioproduction process enables the biomanufacturer to move from a quality-by-testing approach to a QbD approach, which is more flexible (1). By applying advanced sensor systems combined with mathematical modeling techniques, one can gain an enhanced understanding of the processes that produce the biologic product.

In addition, this use of PAT would allow for on-line prediction of the critical quality attributes (CQAs) required to maintain product quality and offer the ability for real-time product quality control.

Mammalian cells are most frequently used as the hosts for manufacturing complex biopharmaceuticals, and cultivation of these host cells is a key factor in the production of biotherapeutics. The cultivation step impacts both product yield and product quality (1).

Because there is a lack of techniques for real-time measurement of product attributes, quality assurance in biopharmaceutical processes still mainly relies
on the repetition of identical process settings and extensive end-product testing.

Even in a bioprocess with identical process settings, however, variability in end-product quality output is still likely to occur due to the variability of inputs, such as the raw materials and the living host cells themselves (1).

Using a QbD strategy that implements PAT offers the advantage of real-time process monitoring and, subsequently, quality control based on the application of multivariate data analysis and mathematical modeling techniques that can help predict product outcome. QbD starts by defining the relevant target product profile and CQAs.

Subsequently, development of the manufacturing process takes into account the likely impact that process parameters will have on process response, using knowledge gained through risk-assessment analysis (e.g., instant failure mode and effects analysis).

Once those steps have been developed, operators can determine the relationships between critical process parameters and product quality attributes by applying statistical design experiments, multivariate data analysis, and mathematical modeling techniques. This will, in turn, inform the design of the operation space and the sensor technologies needed to monitor the critical process variables in real-time (1).

Because the QbD approach aims to achieve closed-loop CQA control, model predictive control (MPC), a methodology used for multivariate control in many other process industries, would be best suited for bioprocessing. The goal of MPC is to meet various CQA specifications by manipulating process inputs while also taking into consideration process constraints.

**REFERENCE**


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**PAT From a Small-Molecule Vantage Point**

Ensuring consistent product quality is also a challenge for small-molecule pharmaceuticals as it is for biologics. How does process analytical technology (PAT) come into play? *BioPharm International* spoke to Ajay Pazhayattil, associate director, Technical Operations Process Validation, at Apotex for some insight.

**BioPharm:** How is process analytical testing adjusted for production scale-up?

**Pazhayattil:** Scale up introduces variability with raw material batches, equipment, and process parameters. Each of the input variables needs to be thoroughly understood in order to maintain the desired quality output. Factors such as PAT instrument reliability, sampling and testing frequency should be re-considered for an at-line, on-line, or in-line PAT system. The evaluation should be conducted as part of process scale-up activities in determining the control strategy for the new scaled-up process.

**BioPharm:** What are the major driving factors for developing more accurate process analytical tests?

**Pazhayattil:** Use of PAT technologies for attributes such as LOD [loss on drying], particle size distribution, and blend uniformity were developed to significantly reduce time and cost for organizations. PAT allows for better product characterization and improves product knowledge. The data can be used in continuous improvement initiatives as well as development of similar products and processes. Future advances in PAT should focus on improving the analyzer functionality and reliability.

**BioPharm:** What is the relevance of PAT where continuous manufacturing is integrated into the commercial manufacturing process?

**Pazhayattil:** With the advent of continuous manufacturing platforms in solid-dose formulation, the application of PAT analyzers has become even more crucial. During a continuous manufacturing operation, PAT signals are utilized as a feedback mechanism to optimize process controls, if required, to achieve the desired quality attributes. PAT therefore reduces the risk of failure in continuous manufacturing. PAT chemometric modeling and instrument accuracy are critical to achieve this goal.

**BioPharm:** What are the major challenges in updating analytical testing practices?

**Pazhayattil:** Adapting new technology, reliability of the PAT instrument, availability of technical skills, method development and qualification, defining acceptable measurement frequencies, incremental initial investments, and management of raw material and process changes, are few of the challenges. The prevalent uncertainty about regulatory acceptance of replacing traditional analytical methods with new PAT methods across multiple markets is one of the major deterrent factors as well.
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Reducing Cross-Contamination Risks in Process Chromatography

Cynthia A. Challener

When first introduced, single-use technologies were cautiously used in R&D laboratories for upstream processing. Today, single-use bioreactors are widely used for biologic drug manufacturing, and downstream disposable technologies for commercial-scale production operations are being introduced and increasingly adopted. Single-use solutions for process chromatography are no exception and offer distinct advantages over permanent, stainless-steel systems in many circumstances.

REDUCING RISK

Manufacturers are increasingly looking for single-use technologies, according to Andrew Bulpin, head of process solutions for MilliporeSigma. “When it comes to new facilities, the small footprint and easy-to-use format of the products reduces investment needs with respect to facility, equipment, and labor, enabling cost savings and faster time to market,” he says. All of the attributes of single-use technologies—reduced process time, faster equipment turnaround, greater manufacturing flexibility, and reduced risk of cross contamination—apply to chromatography, according to Michele Morelli, global product manager for single-use automated technologies at Pall Life Sciences.

“With typical bioprocessing tools, a lot of effort and care goes into cleaning and cleaning validation of contact surfaces since any contamination in the purification process can be detrimental to the manufactured drug,” adds Fredrik Lundström, product manager for bioprocess hardware with GE Healthcare Life Sciences. “The obvious advantage
with single-use technology is that it provides a replaceable fluid path that eliminates the risk of cross-contamination between different molecules,” he notes.

In addition, disposable flow-paths on single-use downstream processing equipment typically come gamma irradiated, leading to better bioburden control, according to Lundström. Preparatory and post-processing steps such as column packing, validation of packed-bed efficiency, verification of endotoxin clearance, unpacking, cleaning of unpacked columns, etc., can also be eliminated with the use of single-use processing tools, leading to increased efficiency and productivity due to a reduction in the change-over times between batches. Elimination of cleaning and cleaning validation activities also leads to smaller and simpler (open ballroom) facilities for biopharmaceutical manufacturing.

Market risks can be minimized as well. “Facilities incorporating single-use technologies provide flexibility not only with respect to the number and types of products they produce, but also market demand, because production capacities can be readily adapted in response to changes in market needs,” observes Bulpin. “It is quite straightforward to add an additional disposable processing line to increase capacity. Furthermore, the manufacturing facility can be utilized for another product after the target yearly supply of the initial product has been achieved,” he explains.

**MULTIPLE APPLICATIONS**

With its inherent benefit of avoiding cross-contamination, single-use chromatography is most suitable for application to campaigned manufacturing of drugs, according to Lundström. “Single-use chromatography is an increasingly attractive option for multi-drug facilities, such as [contract manufacturing organizations] CMOs and [contract research organizations] CROs, because single-use products allow quick facility changeovers and require less resources and facility time for setting up processes and performing manufacturing operations, and are more economical from a capital expenditure viewpoint,” Bulpin comments.

The main drivers for using single-use chromatography systems are batch size and frequencies, according to Morelli. “It becomes a balance between the total cost of operation and manufacturing agility, particularly for multiproduct facilities,” he says. When performing cost analyses, he adds, it is important to consider the cost of additional equipment such as steam generators that are required with stainless-steel equipment.

The flexibility afforded by single-use chromatography can also be beneficial for the production of therapies in smaller volumes, which is important when considering the advancement of personalized medicines and niche products for rare diseases, according to Bulpin. Lundström notes that single-use chromatography processing tools lend themselves to preclinical- and clinical-scale production of drugs where time-to-market is more of a critical consideration than other aspects, such as process economics.

High-potency drug manufacturing and other processes requiring closed processing and/or mini- mization of potent/toxic material in wastewater also benefit from adoption of single-use technologies for process chromatography unit operations, according to Lundström. Bulpin adds that from a supply perspective, single-use products can be adapted to new facilities for at-location processing including nationalized supply or even point-of-care processing, and can support mobile processing paradigms when needed.

**PREFERRED TARGET MOLECULES**

A variety of biologics benefit from the use of disposable technology in their production, from monoclonal antibodies (mAbs) and recombinant medicines to vaccines and novel therapies, according to Bulpin. Typically, adds Lundström, the decision to use single-use or traditional process tools for process chromatography unit operations stems from requirements such as scale of manufacturing and single-product vs. multi-product manufacturing, as opposed to the drug that’s being produced.

Because manufacturing equipment that offers a truly single-use flow path minimizes operator exposure, however, single-use chromatography systems are used in particular for the production of biologic drug substances with high cytotoxic potency, such as antibody-drug conjugates (ADCs), according to Morelli. In Lundström’s experience, in addition to highly potent compounds, single-use technologies tend to be used more often for vaccines and cell/gene therapy manufacturing due to the natures of these target molecules.

**WHEN SINGLE-USE IS NOT VIABLE**

After issues of safety and process economics are considered, technical feasibility determines whether single-use chromatography will be used in a given manufacturing process. In general, disposable systems are not a viable option for facilities that produce significant volumes per year or those that use large stainless-steel tanks for production, according to Bulpin. “Facilities with dedicated production lines for processing a single drug molecule with clear projections of demand requirements will benefit economically from using traditional process chromatography tools as opposed

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to single-use processing tools,” says Lundström.

In addition, single-use process chromatography tools are limited to low-pressure applications, and these tools typically cannot withstand the harsh chemicals used in reversed-phase chromatographic separations.

While scale has been a limiting factor with single-use chromatography, Lundström points to the development of tools that can process reasonably high-titer batches coming from 2000-L bioreactors. On the other hand, he notes that established processes with strict limits on process control parameters may need to use traditional processing tools because the analytical and functional performance of single-use components may not match up to those of traditional components such as pumps or sensors.

HYBRID SOLUTIONS

With single-use systems providing advantages for some, but not all, process chromatography applications, often biopharmaceutical manufacturers use hybrid solutions that incorporate both disposable and traditional stainless-steel technologies.

“There seems to be wide variation in the use of these tools, depending on facility provenance, number of molecules manufactured, regionalization requirements, drive towards standardization, productivity, and process economic considerations, etc.” states Lundström. The goal, he adds, is to “extract the maximum benefit while managing existing and future constraints, leading naturally to a hybrid approach to processing either within a unit operation or across unit operations used in the bioprocessing workflow.” As examples, Lundström notes that single-use chromatography systems are often used with traditional columns, and clean-and-reuse systems can be used with pre-packed disposable columns.

Single-use system suppliers have developed products that are designed to work in conjunction with stainless-steel equipment, according to Bulpin. MilliporeSigma, for instance, offers single-use chromatography membranes designed for high mAb throughput that allow the high loadings often obtained in stainless-steel facilities.

Morelli observes that many biologics manufacturing facilities use a combination of smaller pre-packed columns and re-packable columns at the 1-L size and above because pre-packed columns are not economically viable at larger scales. Often disposable buffer and collection bags are used across all scales. “Chromatography is a case study for the combined application of single-use and reusable components,” he says.

A CONTINUOUS DYNAMIC

Continuous processing has the overall advantage of maximizing production efficiency while minimizing capital expenditures and equipment downtime, according to Morelli, which are advantages shared by single-use technologies. Advances in single-use technology are, in fact, facilitating process intensification and continuous processing.

Continuous chromatography is a technique that many facilities are currently evaluating or plan to evaluate in the immediate future. “When applied to chromatography, such as in the form of simulated moving bed technology, continuous processing allows purification in a continuous mode using smaller columns and exploiting the full resin capacity, with no safety factors to prevent product loss,” Morelli comments.

The complexity of a continuous chromatography system paired with the need for high biobur-
In October 2017, GE Healthcare opened its first 3-D printing lab (the Innovative Design and Advanced Manufacturing Technology Center for Europe) in Uppsala, Sweden. The center combines advanced manufacturing technology such as metal and polymer printers and collaborative robots, or “cobots”, with traditional machining equipment. The company is working with Amgen to test the performance of a custom-designed, 3D-printed chromatography column to determine if it can be used in Amgen’s R&D efforts to develop improved processes for the purification of bio-pharmaceuticals.

THE ROLE OF SUPPLIERS
One important aspect to consider when choosing to use single-use technologies for any part of a commercial production process is the role of the supplier. With single-use tools, more of the typical responsibilities become shared with suppliers, because they not only take responsibility for timely delivery of the equipment and associated consumables, but also of other aspects such as gamma sterilization, validation, documentation, integrity, batch-to-batch consistency, and change control notifications, according to Lundström.

“Users of disposable technologies should ensure that their suppliers have adequate expertise and controls in place to ensure quality, timely supply, and documentation support of the systems they provide. If done right, and if the supplier has implemented robust security of supply protocols, it is possible to optimize ongoing order-receipt and inventory management of single-use consumables. If it is not done right, the savings in footprint and resources resulting from traditional to single-use transition can easily be lost due to expansion of facility space needed to keep consumables in stock for use at the right time,” Lundström observes. ♦

GE Healthcare Acquires Purification Technology
GE Healthcare has completed the acquisition of Puridify, a UK-based bioprocessing start-up focused on a nanofiber-based platform purification technology for biopharmaceutical production, the company announced on Nov. 28, 2017 (1).

The acquisition includes Puridy’s technology, FibroSelect, which is complementary to the bead resins and chromatography membranes used in downstream bioprocessing. The technology offers faster mass transfer, scalability, and ease of use, according to the companies.

Puridy’s technology is the result of collaboration with several major biopharmaceutical manufacturers. The platform is expected to bring productivity improvements in the process development phase and in small-scale manufacturing for a variety of biopharmaceutical applications. GE Healthcare reports it will invest further to commercialize Puridy’s platform and integrate it into the range of bioprocess purification products already available at GE.

Pall Unveils Inline Diafiltration Modules
Pall Corporation introduced the Cadence Inline Diafiltration (ILDF) modules, which provide repeated downstream dilution and concentration cycles without a recirculation loop, for scalable single-pass diafiltration (DF) in continuous bioprocessing (2). The technology was introduced at a Leadership Forum series at the company’s Westborough, MA, center of excellence on Nov. 14–15, 2017.

The modules enable continuous DF processes in ultrafiltration and DF (UF/DF) processing steps and are available in a range of size formats to accommodate various processing volumes. The portable design makes the modules capable of continuous monoclonal antibody downstream purification processing in one or more manufacturing locations.

The company’s standard T-Series cassettes act as the building blocks for the Cadence ILDF module, which is offered with Delta regenerated cellulose or Omega polyethersulfone membranes that provide high flux, high selectivity, and low protein binding characteristics. The removal factor of the module is on the order of ≥ 3-log in a scalable, accurate platform with proven selectivity and low protein binding attributes, according to the company, and the new modules enable significantly reduced system hold-up volume and feature a holderless design.

References

—The editors of BioPharm International
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The Biomanufacturing Technology Roadmap, an industry-wide initiative to accelerate innovation in the biomanufacturing industry, was published by the BioPhorum Operations Group (BPOG) in July 2017 (1). The roadmap focuses on biomanufacturing strategy over a 10-year timeframe and defines the needs of, challenges to, and potential solutions for the industry. With a diverse pool of participants from industry, academia, and regulatory, the roadmap is the result of collaborative efforts.

*BioPharm International* interviewed three members of the steering committee that led the collaborative effort for the roadmap. Rajesh G. Beri is technical director R&D, biomanufacturing, Lonza; Morten Munk is global technology partner at NNE, a pharma engineering firm; and Bert Frohlich is an independent consultant who previously served as director of cell culture process development at Shire Pharmaceuticals.

**DIFFERENT PERSPECTIVES**

**BioPharm:** Why is it important to have the different sides of the industry represented in this collaboration?

**Beri (Lonza):** The biomanufacturing industry has responsibility to bring better, faster, cheaper, and higher quality therapeutics for serving patients. Biomanufacturers are uniquely aware of the challenges faced during development and manufacturing of biologics and they are in the best position to communicate their needs to the sup-
pliers and academic community. It is therefore important to have biomanufacturers involved in [this] collaboration.

In addition, academia plays a key role in conducting fundamental research and pioneering new technologies; suppliers develop and commercialize new technologies; and regulators ensure that new advancements conform to existing guidelines or develop new guidelines in collaboration with industry, if required. Thus it is important to have all four stakeholders involved in the development of the roadmap.

Munk (NNE): I believe all groups have the same common goal, which is to make safe and efficient pharmaceutical available for the patients. The best way to do this, is through collaboration and knowledge sharing. Moreover, the different groups (biomanufacturer, supplier, academia, and regulators) have different perspectives and focus areas in their effort to meet this common goal. Thus, it is important for each group to better understand the perspective of the other groups, and this is best done through dialog and working together on concrete projects.

Frohlich: The initiative started off as a consortium of only major biomanufacturers. More recently, supplier companies and academic institutions have joined. This staged integration was very much the right approach since it was the first time the biopharmaceutical industry came together to collaborate in the pre-competitive space. It took some time for the biomanufacturing community to learn the rules of engagement and to set a common direction.

These companies had the most experience in the direct supply of drug to patients. It was clear from the beginning that the full benefit of the roadmap would eventually only be realized with the participation of the whole biopharma industry, including the supplier community and academia. However, the manufacturers needed some time to speak with one voice and to articulate a vision. Until that point, each company spoke directly to suppliers and academic collaborators individually. Consequently, these supporting communities often received very different messages from many different companies.

The Biomanufacturing Technology Roadmap focuses on a biomanufacturing strategy over a 10-year timeframe.

To find solutions to current obstacles, engaging the supplier community is of key importance especially in more mature technologies that are closer to commercial viability. Likewise, engaging the academic community is key in terms of building a future workforce as well as attacking newer, more novel technologies and applications. By indicating the major and most urgent obstacles to progress in the biopharmaceutical industry through the roadmap, suppliers and academic labs can pursue solutions with greater certainty that what they develop will serve an important need.

Also, right from the beginning, it was realized that the regulatory community should also be engaged at some point and even that the various regulatory agencies should be seen as partners to the evolving roadmap. As a regulated industry, any solution will have to meet regulatory approval before it can be implemented.

ROADMAP BENEFITS

BioPharm: What are the major benefits of this roadmap?

Beri (Lonza): As mentioned previously, biomanufacturers have collectively contributed their challenges and needs and these have been documented in the roadmap. In addition, an assessment was performed with the suppliers and academics to estimate the time required to develop technologies addressing the needs and challenges. Thus, biomanufacturers can use these documented exercises to project availability of newer technologies and determine evaluation/implementation plans for their facilities.

Separately, 12 individual projects have been launched addressing the critical needs selected by member companies. By actively participating in these project teams, biomanufacturers can contribute to project success.

Munk (NNE): The pharma industry is a conservative industry, and very few dare to be the first movers in exploring new technology. The Biomanufacturing Technology Roadmap offers a forum for the “brave” and forward-looking to share experiences and results in their work with innovation. This helps all members to make better business cases in their individual companies.

For example, when presenting a new idea, the first questions quite often are: Who else have tried this? What is the risk? How will the regulatory bodies view this? Through the collaboration in BPOG, it is a lot easier to give convincing answers to such questions. Furthermore, I find it inspiring that members of BPOG have the same passion, drive, and courage as I do to try to make a difference in our industry.
**Frohlich:** The mapping process began with the identification of the major business drivers facing the biopharma industry: speed, flexibility, cost, and quality. The map then was designed to target these drivers using various metrics. While the most relevant metrics are still evolving, they will be useful in identifying specific deficiencies and eventually estimating and realizing the value of a solution.

More importantly, however, is the intrinsic value in a collaborative approach. It is becoming increasingly clear that the cost of progressing various technologies and industry standards is less costly if done collectively than if pursued individually by companies.

**The focus of the Biomanufacturing Technology Roadmap** is on the chemistry, manufacturing, and controls (CMC) side of drug commercialization. For most companies, CMC-based technologies are not differentiating and do not impinge on product or therapeutic intellectual property. The cost of supplying a drug to market is appreciable, and the gain from collaboration in the pre-competitive space is likely to outweigh the apparent competitive advantage of keeping certain practices and technologies proprietary.

Furthermore, there is greater certainty within any organization in pursuing a given direction if it has been vetted with industry colleagues. The roadmap can even help a practitioner convince his or her senior management of the benefits of investing in certain approaches and technologies and at lower risk.

**Evolving Capacity Needs**

**BioPharm:** How would the Biomanufacturing Technology Roadmap remain relevant as the manufacturing technology and capacity needs in the biopharmaceuticals industry continue to evolve, for example, with precision medicines?

**Beri (Lonza):** Fairly early in the roadmapping process, we tackled the anticipated manufacturing scenarios. One of the manufacturing scenarios we determined would be increasingly relevant was mobile and modular facilities. Such smaller scale and portable facilities will increasingly gain importance for delivering precision medicines of tomorrow. In addition, there is ongoing discussion in the BPOG Technology Roadmapping Steering Committee of developing a roadmap with newer biologic modalities, such as gene therapy. Thus, the roadmap will continue to be updated in order to deal with the continuous evolution of the biopharmaceutical industry.

**Munk (NNE):** We are in the middle of a paradigm shift, where the distance between the manufacturer and the patient will get shorter and shorter. Individual patient needs and considerations are going to affect the way pharmaceuticals are produced, shipped, and administered. Closer collaboration between biomanufacturers, suppliers, academia, and regulators are pivotal to fully understand those needs and find the best solutions for how challenges can be met, while still keeping the treatment affordable. BPOG offers a forum to share knowledge of how to incorporate the patient perspective in the way the future pharmaceuticals are delivered to the patient.

**Frohlich:** By definition, a roadmap is forward-looking. It attempts to predict future needs from current trends and obstacles. Additionally, the Biomanufacturing Technology Roadmap should be viewed as a dynamic tool and not a static map. By refreshing the roadmap periodically, its direction will evolve with the industry.

By necessity, the roadmap scope had to be restricted initially. Due to resource limitations within the member companies and BPOG and a lack of expertise in some of the newer biopharmaceutical products and treatment modalities, the first edition of the map could not be all-encompassing. The initial emphasis of the Biomanufacturing Technology Roadmap has been on the manufacture of recombinant proteins and, even more specifically, on monoclonal antibodies (mAbs).

With successive editions of the roadmap, other industry sectors will be addressed. As new therapeutic technologies continue to emerge, the required production technologies will need to be included. To some degree, the need for flexibility in facility design has already been realized. Future facilities will need to accommodate an increasingly wider array of product types to justify the significant capital investments associated with manufacturing capacity.

It is also important to note that the vision of the roadmap is not to be redundant with other industry initiatives but to be complementary. Its role should be viewed as having a coordinating function within the industry as a whole.

For example, the cell therapy sector has already begun its own map; the Biomanufacturing Technology Roadmap would not attempt to repeat or supersede the cell therapy map, but to incorporate what has already been addressed.

Also, many aspects of the Biomanufacturing Technology Roadmap are not specific to any specific manufacturing platform. Issues such as automation standards, supplier partnerships, knowledge management, and new paradigms for real-time release will be of general use and applicability to the industry.
Furthermore, all outputs of the BPOG Biomanufacturing Technology Roadmap will be published to a public forum, and the steering committee is committed to taking input from smaller players and the industry at large.

**REGULATORY ALIGNMENT**

**BioPharm:** How would the Biomanufacturing Technology Roadmap help biomanufacturers align with regulatory standards?

**Beri (Lonza):** The regulatory manufacturing standards will continue to dictate biomanufacturing practices, so any new technologies will have to conform to the standards. However, newer standards may be required due to transformational changes likely to be brought in the move to full digitalization, big data analysis, machine intelligence, etc. Biomanufacturers can thus play a key role in advising regulatory agencies for requiring new standards or guidelines.

**Munk (NNE):** This most important task for the regulators is to assess risk in the broadest perspective. This consideration is best supported from the industry, by addressing the regulators with a common voice, and presented through risk assessments based on a broad perspective from a wide range of players in the field.

This helps the regulators to better understand and evaluate the risk benefit profile of new technologies, leading to an easier path and faster acceptance of improvements in biopharmaceutical manufacturing.

**Frohlich:** As mentioned previously, engaging with regulators at the earliest formation of the roadmap was seen as a critical component. In fact, a ‘regulatory’ sub-team has already been formed, and some informal communication with FDA has begun.

The intention is to keep the agencies informed of the Biomanufacturing Technology Roadmap progress, if not seek their direct input. This is a global effort and thus other national and international jurisdictions will be brought in. For example, there is already a desire to make progress in certain workstreams so that they will be in a position to influence new guidance documents expected from the International Council for Harmonization.

The chief benefit of the roadmap to the industry as a whole is that regulators will hear a single common voice with regard to needs and concerns. Conversely, the industry will hear and interpret the response from the health authorities in a collective manner.

In the prior paradigm, each company asked for advice and each would interpret the advice and/or requirements on their own. It is no wonder that companies seek to comply with the same regulations in very different ways.

**SUCCESS STORIES**

**BioPharm:** The first edition of BPOG’s Biomanufacturing Technology Roadmap was just recently published, but are there any existing scenarios or case studies among the members where this collaboration has already worked, aka, a success story that you can share?

**Munk (NNE):** Several of the member companies have told me that they use the roadmap in their internal strategic technology evaluation work, and the experience and guidance shared in the document helps them to sharpen their development efforts. Furthermore, it is also my understanding that the document and, maybe even to a large degree, the network within BPOG, helps the innovation champions of the individual companies to push their organizations a bit more in the right direction to dare to give new technology a chance.

All new technology initiatives have initial challenges and setbacks, which are difficult to get over, but it helps if it is possible to use experiences from other companies on how they overcame those roadblocks and managed to lead the projects to a successful outcome.

**Frohlich:** The first edition of the BPOG Biomanufacturing Technology Roadmap is already showing some progress and impact in simply acknowledging the need for some standardization in the industry. While this is not a new idea, particularly around single-use equipment and components and in data structures and automation, there is a greater recognition and agreement that these areas should be addressed.

Again, the goal of the roadmap is not to supersede other industry initiatives but to somehow tie them together.

Another initial success is in BPOG’s official engagement with a US public-private consortium. An agreement recently signed with The National Institute for Innovation in Manufacturing Biopharmaceuticals will tie in their vision of the future as well as harness their resources (2).

Such partnerships underscore the mission of the roadmap not to dictate solutions or be redundant with academic pursuits, but rather to inform and collaborate, thereby helping guide the industry forward as a whole and all its players to achieve greater efficiency in supplying drug to patients worldwide.

**REFERENCES**


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The world of pharmaceutical production is changing rapidly, as therapies and global supply chains become more complex. Manufacturers must not only speed product delivery but ensure quality, safety, and efficacy. Success demands consistent discipline and rigor from supply chain and manufacturing operations, as well as programs and procedures that mitigate risk and variability.

This article discusses efforts that have been underway at Janssen Pharmaceuticals for the past few years to help achieve these goals. Corporate leaders wished to create a program with a transparent structure that would allow employees in different functions throughout the company to measure performance against internal benchmarks, but with a clear focus on patients and healthcare providers.

Inspiration for this program came from the Toyota Production System principle, *obeya*. Grounded in pure, fundamental data analytics, this concept is roughly translated as “gathering all the information that is required to make fast, sound decisions that enable robust and sustainable improvements.”

In 2011, Janssen Supply Chain (JSC) used *obeya* to create and implement global, cross-functional reliability rooms (RRs). These centers are designed to analyze data and provide insights for production forecasts, identify planning and risk metrics, and predict trends and areas of improvement across all of the company’s supply chain functions and manufacturing sites.
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So far, Janssen has set up more than 20 reliability rooms across its global supply chain facilities, each with its own set of performance goals. Teams at each facility track goals on a weekly basis to discern new and emerging issues. This approach allows the team to get ahead of and mitigate any supply chain problems in the making.

Once a problem has been identified and addressed, teams collaborate to discover the root cause of the supply disruption and to locate any patterns that might be behind it, sharing these insights to drive action with respective business process owners.

CONTINUAL IMPROVEMENT
This process of continual improvement and internal readjustment allows for consistent and sustainable improvement across the supply chain. It ensures that employees from different functions, each with different perspectives, review performance and escalate issues or near-misses to identify their root causes and identify any risks that might be embedded in future plans.

In the six years since they were first rolled out, RRs have become essential for monitoring the vital signs of the supply chain. They also serve as a forum in which teams can meet and discuss plans for procurement, production, quality, logistics, and engineering. This approach ensures that one plan, executed by one team, delivers against a set of shared priorities.

A central group is charged with discovering systemic issues that affect the supply chain and working with partners at various sites to find robust, sustainable preventative and corrective actions. At the same time, the central RR identifies best practices that can be shared with the company’s supply-chain partners.

A core tenet of the RRs is risk identification and assessment, which are achieved through a stratification of metrics and other factors based around supply balancing. In this approach, supply-chain-performance metrics are monitored against some thresholds for which performance has been correlated to impact. Thresholds then indicate whether or not the problem is under control.

For example, there is a statistical correlation between certain metrics that are associated with stock outs in specific markets, which are fed by certain sites. Knowing these correlations allows targets to be set so that any supply disruptions can be avoided.

Similarly, data have been correlated on the types of product-quality issues and their impact on the supply chain. These correlations, and thresholds, are then used to guide inventory stocking and business continuity planning.

USING DEMAND TO TRACK RISK
Demand and planning can be used to track risk. The RRs, for example, engage in monthly demand reviews to measure and monitor mean-absolute-percent error and bias to forecast.

The company has also introduced a bias-tracking signal that effectively measures and identifies patterns in under- and over-forecasting. Using this signal helps to ensure that the assumptions that are made in business forecasts are regularly and thoroughly reviewed. This review is essential to minimizing variability.

The supply-chain function is utilizing advanced analytical techniques to determine the optimum algorithm for each product and market. For example, for planning, teams typically look at the demand/supply balancing during a 13-week period. When and where gaps in supply or atypical reductions in inventory show up, the RRs raise and review a short-term exception management (STEM) action to address the problem.

Individuals from different functions within the company jointly decide on the best course of action, and results are monitored weekly. In addition, the RRs keep a log of every potential supply interruption, early warning indicator, and critical stock out, tracking each issue and its resolution. So far, data have shown that, if a potential supply interruption can be detected more than eight weeks before it happens, the company will be more than 80% successful in mitigating its impact.

MONITORING SUPPLIERS
Assessment tools also provide a holistic picture of contract partner and supplier risk and performance. The granularity of tracking will depend on the company’s level of dependency on the individual partner. Generally, the RRs track data on suppliers’ quality, delivery, cost and risk profile, technology usage, innovation, audit results, and strategic alignment. In some cases, their internal performance is monitored in terms of capacity utilization, schedule attainment, raw material and work-in-progress levels, as well as audit status.

These data provide transparency and a window into their internal performance, giving early warning signs of possible trouble. Data sharing takes place within a framework of partnership that encourages periodic business reviews and a spirit of mutual improvement.

MANAGING INFORMATION
Currently, RR’s collect data from various sources, including:

* Business data warehouses that store information on commercial performance
* Online portals, laboratory information systems, and enterprise resource planning systems that store product quality data
Procurement systems that provide supplier performance data. These data are then interfaced into an enterprise data warehouse (EDW), using business filters and calculations to derive performance data. The EDW is built on a Teradata platform, and staged data are visualized and analyzed using a number of different software programs, including products from Spotfire, Tableau, Qlikview, and Qliksense.

During the initial planning stages of the Janssen RRs, there were concerns about gathering the data, making them visible, and ensuring attendance from the stakeholders at each site amid busy schedules and eminent deadlines. Gradually, as the teams adopted the approach and started to see and feel the benefits, each team adapted the approach to make it work best for them. Each room has a standard configuration and standard data, but the sites have the freedom to incorporate extra information to optimize their effectiveness and efficiency.

**TRAINING APPROACHES**

Because the company is global in outlook, training for the RRs tends to be built around a central communication or training plan, utilizing short video clips that explain system utilization.

This basic structure is then reinforced with traditional presentations, both self-study modules and interactive. This standard is maintained by a central team and then made accessible via internal networks. Training is also augmented based on local or regional practice to accommodate local needs.

**SUSTAINABLE RESULTS**

Since their inception, RRs have had a measurable impact in preventing supply chain disruptions by allowing the company and employees to visualize any constraints, under-

stand the business from an end-to-end perspective, and drive a more predictive mindset. The RRs solve challenges and problems every day, ranging from missed deliveries from suppliers to accommodating changes in demand to equipment improvements.

One of the issues monitored has been availability and correctness of narcotics licenses that permit sales of some products in regulated countries. Through data collection and analysis, key themes were identified related to timeliness, certain countries’ response rates, and the quality of documents.

A cross-functional team from quality, customer logistics, global planning, and affiliate services, facilitated by the global reliability team, has put in place a revised process, simplified procedures, developed personnel training, and installed performance monitoring on the process. As a result, the company has seen a 35% reduction in issues, meaning more “right-first-time” deliveries from affiliates and less risk of stock outs.

Janssen has seen a number of additional improvements and successes from the RRs. Since 2015, the company has delivered a 100% “launch on time” success rate for new products. This is based on a supply chain that can deliver these new products to customers following regulatory approvals and in the committed timeframe.

As RRs develop, they remain centered around four key principles:

- Commitment and connection to the customer. Think about partners in order to make the best decisions and compromises to support them.
- Ability to see and articulate priorities for the business and the commitments that have been made.
- Performance, and the use of a standard for tracking performance, not only in reliability, but in safety, quality, cost, and impact on customers.
- Progress, looking at progress versus larger goals to ensure that the organization is on track to meet business goals, deliver on the sites’ missions, and launch new products.

Along the way, Janssen has had to revise its original approach. In 2016, for example, the company made functional groups more accountable for reliability so that the supply-chain function could take more of a supportive role.

This has helped the functional teams remain the drivers of the various parts and has meant the solutions have greater internal buy-in, while also supporting broader-based improvement.

The company has also updated the RRs’ daily performance management to standardize them around the Johnson & Johnson production system and values (1), which brings a single standard to all sites. This is being rolled out across the company’s network, increasing the rigor in root cause analysis and execution.

Looking to the future, performance metrics will need to blend both site and supply chain performance. Those metrics, observations, and staff can then be used to identify and eliminate any waste in the system and make sure everything possible is being done to keep products continually affordable.

In the future, the RRs will become increasingly connected and data will need to be collected faster. At this point, RRs are proving to be a key process and capability to help ensure that the organization can predict and visualize issues, rather than simply react to them.

**REFERENCE**

SGS Life Sciences

**Company Description**
SGS Life Sciences is a leading contract service organization providing clinical research services, analytical development, biologics characterization, utilities qualification, biosafety, and quality control testing. SGS provides Phase I-IV clinical trial management and services encompassing PK/PD simulation and modeling, data management, pharmacovigilance, and regulatory consultancy. SGS also offers contract laboratory services (detailed below) that include analytical chemistry, microbiology, stability studies, method development, and protein analysis. SGS is the world’s leading inspection, verification, testing, and certification company.

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WHEN YOU NEED TO BE SURE
Single-Use Bioreactors Pose E&L Challenges

Feliza Mirasol

A roundtable Q&A with biopharma executives elucidates the challenges posed by single-use bioreactor bags in contributing to extractables and leachables in the biomanufacturing process.

The use of plastic bioreactor bags in single-use systems pose their own set of unique challenges for determining the presence and mitigating the risks of extractables and leachables (E&L) in the biomanufacturing process. What are these challenges and how can a manufacturer troubleshoot the problems that can affect product quality and efficacy?

BioPharm International interviewed Derek Wood, associate director, Extractable/Leachable and GC/MS Services at PPD Laboratories; James McLean, manager, Analytical Science at Catalent Pharma Solutions; Andreas Nixdorf, business development manager at SGS Life Sciences; and John Iannone, director, Extractables/Leachables & Impurities at AMRI to get their take on the vulnerability of single-use bioreactors to E&L.

BIOREACTOR VULNERABILITY

BioPharm: Are single-use bioreactors, which are typically comprised of plastic, vulnerable to contamination by E&L material, and how vulnerable are they?

Wood (PPD): Extractable/leachables evaluation for all types of components used in biopharmaceutical single-use system manufacturing components, including single-use bioreactors, is an important consideration and is a hot topic in the industry.

The advantages of the disposable manufacturing process for biologic production are well understood, but, unfortunately, many of the elastomeric
and polymeric components used in such processes, such as plastic films used in bioreactors, are more likely to contribute impurities in the form of leachables compared to more traditional, fixed manufacturing equipment components. Leachables from single-use component materials may propagate to the final drug product and potentially present a direct health risk to the patient, but, even more likely for biologics manufacturing especially, a key concern is the potential for leachables to alter the quality and efficacy of the product itself.

A single-use bioreactor utilizes a disposable bag in place of a fixed culture vessel. Such bags typically are constructed of multi-layer, polymer films, incorporating the use of a middle barrier layer (for example, ethylene vinyl alcohol) sandwiched between an inner film, such as polyethylene, that has direct contact with the cell-culture media, and an outer layer film designed to impart structure/strength and durability. The outer layer material may be, for example, a modified form of polyethylene, nylon, or polyester, and the three layers are bonded together in the material manufacturing process.

The film material types for the different layers will vary based on the supplier. For example, in some cases, the inner layer may be polypropylene with polyvinyl alcohol as the middle layer.

**McLean (Catalent):** The single-use bioreactor system (SUS) is more susceptible to extractables due to the nature of the materials of construction. These SUSs are designed to be highly flexible. In order to achieve the desired flexibility, the materials of construction tend to be polymers with lower levels of crystal-line structure, such as low-density polyethylene (LDPE), which would facilitate higher diffusion of chemical species, such as plasticizers, antioxidants, thermal stabilizers, slip compounds, and monomers. This is further exacerbated by the intended use of the SUS.

Historically, manufacturing and in-process equipment involved transient contact times with the API and/or drug product media measured in minutes to hours. For SUSs, their contact time may be days, or, in the case of intermediate bulk storage, years. These extended exposure conditions serve to make the extractable potential a higher risk.

**Nixdorf (SGS):** Plastic bags are often made from different film layers that can be made with different resins, each of which has a unique combination of properties that makes it ideal for certain applications. For example, low-density polyethylene film acts as a gas barrier, which is necessary for drug packaging because the drugs would quickly spoil if exposed to oxygen. Polyvinyl chloride film, on the other hand, is gas permeable, but an excellent barrier against moisture.

Polyester films can be used as mono films for pharmaceuticals requiring low moisture barrier, or they can be integrated into barrier structures. Plastic films also can be clear or colored, printed or plain, single- or multi-layered and combined with other materials, such as aluminum and paper. For bag construction, multi-film constructions are mostly used. Thus, depending on the bag construction, leachables can be originated from different polymer sources.

**Iannone (AMRI):** [Single-use] reactors are certainly vulnerable to imparting E&Ls into the contents of the bioreactor cell-culture medium. Depending on the additives that are needed for the bioreactor bag, there are a number of different compounds that can leach out and be present within the cell-culture medium. An example, which was published in a scientific journal (1), is a very well documented finding where Chinese hamster ovary (CHO) cells used in bioreactor bags, under a specific instance, were dying off.

It was later discovered that, in the post-gamma-irradiation of the bag, a leachate derived from one of the antioxidant’s breakdown products was producing a compound that was responsible for killing off the CHO cells, even when the compound was present at very low levels. While it wasn’t of toxicological consequence to the patient, it still had a significant impact on bioproduction at that early stage and was affecting the efficacy of the process.

Another point to consider is that single-use-bioreactors are typically very large bags that expose an abundant surface area of the polymer to whatever it is that is in the bag. As the surface area of the material increases, so does the potential for leaching out various additives, breakdown products of the additives, breakdown products of the polymer itself, and different residues from the process.

The high surface area certainly increases the vulnerability for this leaching to occur, although larger bags typically will result in a lower bag material surface area to content solution volume ratio. This ratio suggests the concentration of a leachate would be lower, regardless of the increased probability.

The type of product that is contained within the bioreactors also can have a direct effect on the leachability of some of those compounds. Extraction propensity and solubility play a significant role in what will come out. Furthermore, time and temperature can drive leachates. When talking about bioreactors and cell culture, it is desirable to optimize the conditions for those cells to behave in the way they are intended to in order to produce the desired product efficiently. Typically, they operate with slightly elevated temperatures—about 37°C—to optimize cell...

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E&L Challenges
— Contin. from page 45

proliferation, and with that slight elevation in temperature, they increase the potential for extractability. All of these different factors or parameters play a role in how vulnerable these systems are.

One additional point to consider is that bioreactor bags tend to be more amorphous in nature in terms of the polymer. The more amorphous the polymer is, the more amenable it is to allowing leachates to diffuse from the polymer into its surrounding environment.

E&L TESTING

BioPharm: At which stage(s) of the biomanufacturing process is testing done to determine the presence of E&L, and what can be done about it in real-time if detected?

McLean (Catalent): An effective risk management and risk mitigation is essential to the effective control of extractables associated with any biomanufacturing process. This should be a product control lifecycle strategy with equal focus on the three critical tiers of materials, container closure, and processing systems and drug products.

For raw materials (both product-related and manufacturing), it is vital to ensure processes exist to monitor precursor material controls, material controls, service level agreements with vendors, periodic evaluation of control monitoring methodology, and a robust requalification program. For drug products, major considerations should be the drug product method development and validation, appropriate stability testing, toxicological assessments on an ongoing as needed basis, and a qualification process for unknowns. And for the container closure system and SUSSs, one must ensure it is possible to fully characterize and understand the materials of construction and their associated extractables. This may take the form of controlled extraction studies, simulation/migration studies, and drug-device interaction studies.

Nixdorf (SGS): At those production steps where accumulation of leachables is expected, sampling should be performed and leachables monitored. This should become part of any process qualification.

The profile from different sampling points may be mapped, with the leachables profiles that have been generated after the last filling step. This is to assure that no leachables have been accumulated over the process line. In some cases, target analysis by use of semi-validated methods must be performed to assure that any expected leachables of toxicological concerns have been purified from the process stream.

The sampling strategy depends on the individual biopharmaceutical process and how trustable the single-use components are chemically characterized. A poorly characterized chemical profile in a SUSS component poses a higher risk to the process.

Iannone (AMRI): In biomanufacturing processes, people look for the presence of E&Ls through the entire process from the earliest biomanufacturing steps to the very end of the process and all stages in between. Testing is done at multiple stages of biomanufacturing in order to understand how each individual component of that process will have an effect on E&L. In the case of the bioreactor, it is very far upstream in the process—very far from the patient—so it typically has a very minimal impact on safety. E&L should be understood as a function of risk, which needs to be characterized and controlled throughout the entire process.

Regarding what can be done in real-time, there is a lot of innovation going on right now where people have the ability to sample a product throughout bioproduction. They can do different tests that allow one to make modifications based on those results, whether it be a simple total organic carbon content measurement or even just a sampling where one would perform some of the traditional methods used in E&Ls testing such as gas chromatography–mass spectrometry (GC–MS) tests or other analytical techniques. Again, it goes back to the risk characterization and determining what matters most when evaluating E&L impact. There is no one-size-fits-all approach.

MANUFACTURING CONCERNS

BioPharm: How much of a concern is E&L in biomanufacturing compared to traditional small-molecule pharmaceuticals, for example?

Wood (PPDI): As noted previously, the single-use biomanufacturing process that commonly is used for production of large-molecule products increases the amount of direct contact of the process stream with polymeric and elastomeric component materials. That results in a higher degree of overall risk for leachables being introduced to the product, which may interact directly with the product or which may potentially pose a safety concern directly to the patient.

Leachables often present a greater concern in general for biologic and other large protein molecules compared to small-molecule formulations, and this greater concern for large molecules applies as well to leachables that may be introduced from the biomanufacturing process.

There are multiple reasons why large molecules may present a greater concern for leachables. The large size and complex, conformational structure of proteins provides a higher surface area and an increased number of potential active sites where leachable compounds (organic or inorganic) may interact with the protein.
Large-molecule formulations often include solubilizing agents such as polysorbates, which may hasten migration of organic leachables by improving the solubility of such organic compounds in an otherwise typically aqueous medium. The amphiphilic nature of proteins themselves also may hasten the solubilization of organic leachables.

Nixdorf (SGS): In all production lines where stainless steel has been used, the leaking problem is a lower risk compared to processes where single-use technology has been used. Large-molecule formulations are composed of more complex matrices, which may contain surfactants such as polysorbate or poloxamer or related substances that could easily interact with plastic surfaces.

It is often very challenging, or not possible, to discover leachables at trace levels in that “chemical cocktail” by screening methods (not targeted analysis). Complex sample preparations are generally required for biological formulations and there can be issues associated with the recoveries of leachables in the biological matrix. Proteins could easily capture or bind with lower mass leachables and they do not release them in solution again. Thus, these leachables would run out of the analytical window. In small-molecule manufacturing, discovering of impurities is much more easily performed.

Iannone (AMRI): Because a biologic is a larger molecule and has multiple reaction sites, the presence of other chemical constituents like E&L will have a higher potential for reacting with the biologic, and having some impacts either on the efficacy of the product or on safety to the patient.

The way biologics are made—using single-use systems and having various polymeric systems exposed throughout the entire process—is not as common in small-molecule manufacturing. For small molecules, the manufacturing process traditionally uses glass or stainless-steel reactors. By having fewer polymers exposed, the source of E&L is reduced dramatically.

E&L is a much higher concern for all of the reasons that I just referred to and needs to be characterized accordingly when considering the manufacturing of biologics. The best way to do that is through a comprehensive risk management process followed with appropriate chemical characterization. The trend in recently developed regulatory guidelines reinforces this approach.

REFERENCE

2017 Employment Survey
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Respondents also expressed opinions about factors that would motivate them to change jobs; intellectual challenge (33.4%), work/life balance (30.2%), and professional advancement (29%) were the top factors. Non-financial incentives were singled out as “the main reason I come to work.” Respondents ranked intellectual stimulation (32.1%), challenging projects (33.1%), and the company’s potential for success (27.2%) as the top reasons.

Low pay, however, was noted by 19.3% of respondents as the leading sole factor to leave a job. Other top reasons cited include discrimination (16.6%), negative workplace attitudes (16.6%), and issues with management (13%).

DISILLUSIONED WORKFORCE?

The survey revealed a growing desire to seek new employment. More than half of the 2017 respondents (59.3%) “agreed somewhat” or “agreed strongly” that they would “like to leave their job, given the opportunity,” up from 54.5% in 2016. More than one-third said they were “likely to leave my job voluntarily in the coming year;” almost 15% expected to leave their job involuntarily. Nearly 30% said they would like to change careers and leave the biopharma industry.

While the desire to change positions is strong, the number of people actually changing jobs is significantly less. In 2016, 17.1% of respondents reported a voluntary job change; in 2017, that number moved up slightly to 17.3%.

Respondents assessed a tougher path to finding a new position, compared with 2016; 17.1% said it would be straightforward to find a comparable new job; 46.4% said it may take a while, but they would be able to find a comparable position. More than 22% said it would be straightforward to find a job, but the new job probably would not be as good as the current position; 14.3% anticipated a difficult search and they would have to take whatever position was available.

REFERENCES
Lyophilization, or freeze drying, was a crucial development in pharmaceutical manufacturing, because it allowed heat-sensitive vaccines, antibiotics, and protein-based drugs to be dried safely. The process results in powders with long shelf lives that can be reconstituted at the point of use. Its strategic importance continues to grow, as injectable biopharmaceuticals become a more prominent part of the overall drug market. In 1998, lyophilized pharmaceuticals accounted for 11.9% of all new injectable or infusible drugs, but, by 2015, they made up half of all such new drug introductions (1).

Yet, the basic pharmaceutical freeze drying process has seen little change since it was introduced in the 1940s (lyophilization made a considerable difference during World War II in allowing medicines such as penicillin [Photo] to be shipped long distances and remain stable). According to experts who work in the field, lyophilization remains one of the most time-consuming and expensive of pharma’s unit operations, with energy efficiency of less than 5%, dominance of open loop processing, and lack of inline quality monitoring technology (2).

To help reduce variability and develop more uniform, consistent, and efficient lyophilization processes, the National Institute of Standards and Technology funded the Advanced Lyophilization Technology Hub (LyoHUB) as part of its advanced manufacturing technology consortium in 2014. Based at Purdue University, its members—14 pharmaceutical manufacturers and equipment vendors, as well as universities, independent consultants, and scientists with regulatory agencies—are developing more modern approaches to lyophilization equipment design, analytics, instrumentation, training, and control. The group launched a demonstration facility at Purdue University in 2016 to

**Modernizing Lyophilization**

Agnes Shanley
facilitate R&D and pilot testing. In September 2017, LyoHUB released a 10-year technology roadmap for pharmaceutical freeze drying (2). The roadmap reflects the opinions of more than 100 industry and academic experts whose views were elicited, analyzed, and summarized using methods developed at Cambridge University (3).

LyoHUB members currently view the development of sensors and instrumentation, and process models for primary drying as key short-term priorities for the industry. They have also been focusing on publishing “best practices” papers in open-access journals, to get beyond what scientists describe as the “Because it has always been done this way” hurdle. One of the first white papers describes best practices for process monitoring (4).

**INHERENT COMPLEXITY**

Part of the reason why pharma may still be on a learning curve in understanding lyophilization is because the process is so complex compared with other pharma operations. “Lyophilization involves complex heat and mass transfer,” explained Alina Alexeenko, Purdue University professor of aeronautics and astronautics and co-director of LyoHUB, in an April 2017 webcast (5) on the use of modelling in lyophilization. Some heat-transfer processes are pressure dependent and others can be very sensitive to differences between container types and even to the finishes on the surfaces of vials, she noted.

LyoHUB is advocating greater use of modeling and simulation, including advanced modeling tools such as computational fluid dynamics (CFD), which can offer more detailed views of what’s happening in the equipment than sensor information alone, showing important details about vapor concentration and temperature and pressure distribution, Alexeenko said.

For example, Alexeenko recalled one industrial-scale lyophilizer design. Using modeling, researchers found that a relatively short section of clean-in-place and steam-in-place piping, which accounted for only 3% of the equipment’s area, was causing a 20% reduction in vapor flow rate and overall throughput.

Among other goals mentioned most prominently in LyoHUB’s roadmap are:

- Development of continuous or semi-continuous processes based on technologies. Over the past few years, the food industry has moved to continuous operations, resulting in gains in product uniformity. LyoHUB members expect the same to be possible for pharmaceuticals.
- Use of improved heating methods involving infrared heaters or volumetric heating via microwave, which would allow for closer control of the process.
- Use of spray-freeze drying, particularly for making bulk APIs.
- Alternative sterilization methods, such as hydrogen peroxide and cold-plasma sterilization. Steam sterilization, using steam at temperatures above 120 °C, can result in equipment wear. In addition, the typical sterilization process can take more than six hours to complete. LyoHUB members plan to evaluate lower-temperature alternatives.
- Establishment of standards for characterizing lyophilization equipment performance, which would facilitate scaleup using different vendors’ equipment.
- Better process control, especially during the primary drying stage, during which the ice crystal structure is set, and with it, mass transfer and drying rates. Currently, control is based on traditional open-loop approaches. As a result, such variables as product temperature, drying rate, and residual moisture content are not monitored directly, so any deviations from optimal levels may not receive enough attention.
- Development of process analytical technology (PAT) tools, which will be required for closed-loop control.
- Improved container and closure systems. Currently, product is freeze dried in glass vials with rubber stoppers. LyoHUB is evaluating the use of plastics and developing data on the chemical and physical interactions between pharmaceuticals and containers. Among other plans, the group is considering using vials or stoppers that have been embedded with sensors to monitor temperatures and pressures during processing and transport.

Farther off in the future, LyoHUB is evaluating freeze drying’s use with novel therapies such as cell- and gene-based therapies. Below are some recent developments that have taken place within the roadmap’s focus areas.

**SPIN FREEZING AND MINIATURE MASS SPECTROMETERS**

For the past few years, RheaVita, based in the Netherlands, has been working on a continuous lyophilization process based on spin freezing. Collaborating with Ghent University, researchers have developed a prototype to develop comparative process data (6). They recently presented a model and theoretical design space for the continuous process (7).

In November 2017, Atonarp, an instrumentation company in Toyko, and IMA Life North America commercialized a lyophilizaton-monitoring platform based on research that the two companies did with Pfizer (8). Driving the technology is Atonarp’s miniature
Lyophilization — Contin. from page 51

mass spectrometer, which is said to take up less than half a cubic foot of space. The device offered benefits in monitoring the presence of silicone oil (a sign that heat transfer fluids are leaking from lyophilizer shelves). Researchers also used the device successfully to detect endpoints for primary and secondary drying and to detect vacuum leaks.

WIRELESS SENSORS AND HEAT-FLUX SENSORS

Other process-monitoring solutions developed for lyophilization include IQ Mobil’s Tempiris wireless temperature-monitoring technology, as well as Millrock Technology’s measurement platforms based on heat-flux sensing (9). CorioliPharma has evaluated heat-flux sensing as a PAT technique for lyophilization (10) and found that it provided more insights into drying thermodynamics and allowed them to use a “vial heat-transfer coefficient” to monitor product temperature throughout primary drying.

Advances are also being seen with Tunable Diode Laser Absorption Spectroscopy (TDLAS). One platform that has been optimized for pharma freeze drying uses a spectrometer from Physical Sciences, Inc., and SP Scientific’s LyoFlux analyzer.

REFERENCES

condition that the purchased SOP is reviewed and the appropriate changes be made to reflect the actual operations of the company who purchased the SOP. Failure to tailor purchased SOPs to the actual specific process will most likely result in a regulatory citation for failure to follow written procedures.

SOP FORMAT
Another consideration for an SOP is the format for communicating the information. A company needs to keep an open mind to various SOP formats and communication types. All SOPs, regardless of format, should offer clear step-by-step instructions and may utilize various presentation styles as a means of communicating the details of the SOP. The following examples are presentation styles to be considered when writing SOPs:

• General description: This describes in paragraph form the necessary elements that need to be performed to successfully execute the SOP requirements.
• Play script: This is a simple step-by-step instructional SOP. Its format is a written set of instructions with a logical sequence flow (operator does a, then b, then c, etc.). It is similar to following a recipe for making a cake. The majority of SOPs utilize this type of format.
• Flow chart: A flow chart SOP translates the elements of the written step-by-step instructions into a sequence of pictures that define what is needed to perform the operation in the defined sequence of steps displayed in the flow chart.
• Pictorial: A pictorial SOP uses only pictures to communicate to the user the appropriate steps in the SOP and the order they are to be performed. This type of SOP can be useful when there are language concerns.
• Combination: A combination SOP uses multiple methods, such as both words and pictures, to communicate to the user the critical information in the SOP and the order in which the steps are to be performed.

TRAINING FOR EFFECTIVE SOPs
The final consideration for effective SOPs is training. The traditional read/understood acknowledgement may not be enough to assure that an employee understands the content of the SOP. Companies should consider group trainings and comprehension evaluations for determining the effectiveness of the SOP. Keep in mind, however, that just because an employee does not pass an SOP comprehension test does not necessarily mean the employee doesn’t understand. It could be an indication of a poorly written SOP or ineffective training. Companies should also consider training on SOPs through the use of video recording. This could include presenting video demonstrating proper technique as well as using video recordings as on the job training tools to evaluate proper technique of an individual. The use of video recording could be most helpful for people who need to gown appropriately to enter into an aseptic manufacturing area.

Remember there is no set rule dictating the format of the SOP instructions, and it is up to the company to determine what works best for your facility. SOPs should be written to reflect a company’s business practices, allowing them to optimize efficiency and productivity of their operations. It is important to tailor your procedures to the personnel performing your operations whether highly experienced or relatively new to the regulated environment. The training on an SOP is equally as important as the information contained in the SOP, and companies need to consider the most effective way to train personnel on an SOP. The training presented may not be the same for all SOPs. Bottom line, SOPs and the associated training should be easily understood and able to be followed by the employees who rely on them to perform their job responsibilities.

SOPs and the associated training should be easily understood by the employees who rely on them to perform their job responsibilities.
Q: I recently transferred to the document control department and am working with people on creating and/or revising standard operating procedures (SOPs). My colleagues have very different ideas on how much information should be included in the SOPs. Some want very detailed instructions and others want minimal information. Can you please advise on how detailed SOPs should be to fulfill regulatory expectations?

A: There is no right or wrong answer regarding how much or how little information should be contained in an SOP. Whether you work in the medical device, pharmaceutical, or bio-technology industry, you are relying on SOPs to help you perform the day-to-day activities associated with your job. The purpose of an SOP is to define the steps, in logical order, needed to perform a repeatable task and achieve a repeatable outcome. SOPs document the steps of key processes to help ensure a consistent, quality output. SOPs are useful tools for operationalizing, optimizing, and communicating important corporate policies, government regulations, and best practices for ensuring consistent, reliable, and safe medications or medical devices to patients.

SOPs should be written to allow your personnel to conduct operations in a consistent manner that will assure regulatory compliance and product quality. They need to reflect a company’s specific manufacturing or other operations. The more repeatable and consistent an operation or procedure becomes, the less waste there will be in the process. Consistency in work performance will lead to fewer deviations and investigations associated with the process, which translates into less down time and fewer product rejections. This is just good business sense.

REGULATIONS AND SOPs
SOPs should not be written for regulators, but should reflect a company’s operations. Writing SOPs to appease regulators or because you think the regulatory authorities require them will only lead to confusion and regulatory citations. Writing an SOP for a process, procedure, or operation that you do not perform just because it is listed in the regulations is not advised. This concept is particularly important when taking into consideration today’s environment. They are many virtual and small companies that outsource much of their operations. US 21 Code of Federal Regulations (CFR) 200.10 discusses the relationship between a contract provider and a contract giver by stating, “The Food and Drug Administration is aware that many manufacturers of pharmaceutical products utilize extramural independent contract facilities, such as testing laboratories, contract packers or labelers, and custom grinders, and regards extramural facilities as an extension of the manufacturer’s own facility.” Companies that outsource all or some of their operations should rely on their quality agreements and the SOPs of their contract providers to define how they perform the services being outsourced. Contract providers should not write an SOP that defines something they are not doing that they have contracted for another entity to do.

Some companies, in particular start-up companies, might be tempted to purchase pre-written SOPs. This activity might be acceptable on the...
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