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# BioPharm International

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

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**Number 1**  
**January 2018**

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Milestones Mark Progress and Challenges

The biopharmaceutical industry hit a milestone in 2017 with FDA's approval of the first gene-therapy drugs, demonstrating the innovative capacity of a research-driven industry. Just two years prior, FDA approved the first biosimilar drugs, illustrating the growing pains for a maturing market when generic drugs join innovator products.

In 2018, BioPharm International will mark 30 years of publishing science and business news for the biopharmaceutical market. Throughout the year, and in a special issue published in July, the editors will note key phases of development in the industry, and the challenges ahead.

Some immediate challenges are outlined in the 2018 Biopharma Outlook in this issue. Following the first year of the Trump administration, people have learned to expect the unexpected. The confirmation of Scott Gottlieb as FDA commissioner provided some stability for the agency, as did renewal of the user fee programs. The slashing of corporate taxes at the end of 2017 promised more financial options for bio/pharma companies. However, uncertainties surrounding the healthcare reform and funding for Medicaid and children's health programs lingered as 2018 began.

While such macro events may be beyond the control of most biopharma professionals, those that work in drug development formulation, and manufacturing see daily business operations up close and form opinions about the outlook for 2018.

Outlook from the front line

BioPharm International sampled opinions of biopharma professionals from around the world (1) about trends in the industry and future business prospects. Overall, business activity at respondent companies was stable from 2016 to 2017. Approximately the same number of respondents said business increased compared with the previous year (45.3% in 2107 vs. 46.2% in 2016 (2). However, more respondents (17.5%) said business at their company decreased in 2017 compared with 2016 (14.1%).

The most significant change was the decline in the number of respondents reporting business expansion, 16.1% in 2017 compared with 21.2% in 2016. Fewer people reported business closures in 2017 (2.9% vs. 4.7% in 2016), but more 2017 respondents (15.3%) reported downsizing compared with 12.7% in 2016.

Respondents were slightly less upbeat about the prospects of business improvements at their companies; 51.8% predicted that their company’s business would improve in 2018, compared to 52.4% predicting improvements for 2017. The percentage predicting business would decline in the next year (17.5%) was somewhat higher than the previous year (12.7%).

Prognosis for the industry

The one-year outlook for the biopharmaceutical industry as a whole was a bit more positive compared with the previous year. More than half (54.7%) of respondents said business would improve for 2018; 51.7% expected improvements in 2017.

For the longer term (five years), respondents were less optimistic than the previous year. Almost two-thirds (64.7%) of respondents to the 2017 survey expected business to improve over five years compared with 68.5% reporting long-term improvement in 2016.

References


Rita Peters is the editorial director of BioPharm International.
New Approach for the CAR-T Cell Therapy Treatment of Cancer

Research from Osaka University has revealed a new target for the treatment of cancer using monoclonal antibodies (mAbs). The new strategy was discovered by reevaluating the antigens typically targeted by mAb-based treatments using chimeric antigen receptor T-cell (CAR-T) technology, which has proven to be effective in the treatment of solid tumor and blood cancers.

The study, published on Nov. 6, 2017 in *Nature*, focused on multiple myeloma (MM), a cancer that forms in a type of white blood cell called a plasma cell (1). The antigens that arise from cancer-specific mutations of cell-surface proteins have been thought to be desirable treatment targets. According to the study, however, the targeting of such antigens is impractical because of the diverse variety of these proteins within and between individual tumors, which makes identifying new cancer-specific target antigens challenging.

Subsequently, the university research team believed new epitopes, which are the part of an antigen recognized by the immune cells, could be determined by searching for cancer-specific mAbs and characterizing the antigens recognized by those mAbs.

According to lead author of the study, Naoki Hosen, in a university press release, the need for advances in treatment resulted from the rate of attributed cancer relapses, which lead to the team applying this new-found strategy to identify novel therapeutic targets for MM (2).

The team screened more than 10,000 mAb clones known to work against MM and identified MMG49 as a MM-specific mAb specifically recognizing a subset of integrin β7, a cell-surface receptor that enables cell-extracellular matrix adhesion. The study found that MMG49 reacted to MM cells, but did not react to other bone marrow cell types in MM patient samples. This finding drove researchers to design a CAR that includes a fragment derived from MMG49. The resulting MMG49 CAR T was found to have anti-MM effects without damaging normal blood cells.

According to study coauthor Yukiko Matsunaga, in the press release, results also demonstrate that the active conformer of integrin β7 can serve as an immunotherapeutic target against MM, even though the expression of the protein itself is not specific to MM (2). Matsunaga also explains that these findings support the probability that there are other cancer immunotherapeutic targets that have yet to be identified in many cell-surface proteins that undergo conformational changes, even if the expression of the proteins themselves is not cancer-specific.

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1. N. Hosen et al., *Nature Medicine* online, DOI: 10.1038/nm.4431 (Nov. 6, 2017).

mAbs Against Zika Show Promise

Research by the University of Miami and The Scripps Research Institute has led to the development an antibody-based Zika virus therapeutic that protected monkeys from infection. The study, published on Oct. 4, 2017 in *Science Translational Medicine*, was conducted using blood samples from a patient previously infected with Zika virus (1). Researchers believe that this antibody combination will be safe enough for administration to pregnant women and likely to cross the placenta, protecting both the pregnant woman and fetus from the virus.

The scientists, funded by the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health (NIH), isolated immune cells from the patient’s blood and used them to make 91 mAbs. They identified three antibodies that bound to the virus surface proteins, and each neutralized the virus. The researchers then administered a combination of these antibodies to a species of Old World monkey called rhesus macaques, and exposed the animals to Zika virus one day later. During the 21-day study, all four monkeys who received the antibody treatment showed no virus replication.

The testing of this concept is anticipated through the persuasion of human participants, according to a NIH press release (2). Additionally, the study included collaborators in the United States and Brazil.

References

Binding Site Expands mAb Portfolio

Binding Site’s Immunologicals Group has expanded its mAb product offerings (1). In addition to the established conjugated and unconjugated versions of the IgG4 Clone-HP6025 and the CD23 Clone BU-3438, Binding Site has introduced a number of new mAbs targeting infectious diseases, including cytomegalovirus, hepatitis (A, B, C, and D), herpes, HIV, rubella, and toxoplasma.

These antibodies are highly specific and demonstrate high levels of purity, extended shelf-life stability, and lot-to-lot consistencies, according to Binding Site. The infectious disease mAbs are all available in a standard-sized 1.0-mg fill format, while the rest come in a standard 0.2-mg fill format. In addition, bulk packaging and customer-specific packaging options are available for all of these mAbs.

Reference
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Advances in science captured the biggest biopharma headlines in 2017, with FDA’s approval of two cell-based chimeric antigen receptor (CAR)-T cell therapies. The approvals of Kymriah (tisagenlecleucel) from Novartis on Aug. 30, 2017 and Yescarta (axicabtagene ciloleucel) from Kite Pharma, a Gilead Company, on Oct. 18, 2017 marked a next step forward in personalized medicine. The approvals also signaled a shift in manufacturing from traditional, large batch bioprocessing to an individual patient manufacturing model.

Despite these scientific successes, financial and policy issues once again may be the dominant factors in the biopharma industry outlook. Looking back to the first weeks of 2017, uncertainty was the underlying theme as the industry waited to see how the political agenda of the incoming Trump administration would affect healthcare reform, drug pricing, R&D investment, and regulations.

In the ensuing 12 months, the industry witnessed a record number of drug approvals, including a new commissioner at FDA, a major overhaul to US corporate tax structure, and the announced move of the European Medicines Agency to Amsterdam. Unfinished business—open questions about the fate of the US healthcare system, an unresolved federal budget, and ongoing debate over drug pricing—have extended the air of unpredictability into 2018.
POLITICS, TAXES, AND DRUG PRICES

Efforts to replace the Affordable Care Act (ACA) failed in 2017; only one component, the individual mandate, was repealed as part of the Tax Cuts and Jobs Act (TCJA) of 2017. The Congressional Budget Office estimated that by 2027, 13 million fewer people would have insurance coverage if the mandate were repealed, potentially reducing the number of patients seeking prescription or generic drugs (1). Fewer insured patients could translate into a decline in drug sales. In addition, the future funding for Medicaid and children’s health programs remained uncertain at the beginning of 2018.

Thanks to the overhaul of the tax system enacted in late December 2017, US-based bio/pharma companies started 2018 with a lower corporate tax rate, lower taxes on income earned abroad, and simplified rules for expensing new investment purchases. What biopharma companies will do with the tax savings or repatriated funds—invest in R&D, return it to stockholders, or shop for acquisitions—was not clear as 2018 began.

The tax law overhaul had one negative element: the orphan drug tax credit was reduced from 50% to 25% of qualified research and clinical testing activities.

GREAT EXPECTATIONS

Through the third quarter of 2017, pharma and biotech transactions declined for a second year compared with the active markets of 2014 and 2015, according to Evaluate Pharma (2). The decline was attributed to uncertainty over tax law changes.

Companies with legacy drug products in large therapy areas may spur mergers and acquisitions activity to refill pipelines. In the report, experts noted that early-stage companies developing immune-oncology drugs were overvalued, creating a “seller’s market.” The valuations of large-cap biotech companies were depressed, the report argued, creating opportunity for now cash-rich pharma companies to make a large acquisition.

Strong financial markets also could spur more initial public offerings; small biotechs may also look to independently fund later-stage development, the report authors note.

INNOVATION DRIVES APPROVALS AND INVESTMENT

Despite a decline in the number of drug approvals in 2016, the US drug market is on an upswing; 46 new molecular entities were approved in 2017 compared with 22 in 2016. FDA’s accelerated approval pathways continue to cut review and approval times. FDA also approved five biosimilars in 2017, however, legal action delayed the marketing of some approved products.

FDA’s fast track, breakthrough therapy, accelerated approval, and priority review pathways continue to reduce review time and expedite approvals (3). Some analysts have suggested greater leniency on the part of FDA has contributed to the increase in approvals, a notion the agency denies (2).

PhRMA notes that 240 immuno-oncology treatments are in development, including adoptive cell therapies, bi-specific antibodies, cytokines, immune checkpoint modulators, oncolytic virus therapies, and vaccines (4). Research in immuno-oncology therapies will be closely watched, Evaluate Pharma reports, and could be targets for investment.

COST OF INNOVATION

Although promising platforms such as gene therapies are emerging, the challenge for bio/pharma is to develop these platforms in an efficient way to create “near-term value for all stakeholders,” according to the authors of Deloitte’s annual study on industry return on investment (5).

The report—based on analysis of estimated return on investment from late-stage pipelines of 12 large-cap biopharma companies—noted that projected R&D returns continued to decline from 10.1% in 2010 to 3.7% in 2016 and 3.2% in 2017. The average cost to bring a drug to market continued to increase from $1.188 billion in 2010 to $1.992 billion in 2017.

What will biopharma companies do with the tax savings and repatriated funds: invest in R&D, reward stockholders, or shop for acquisitions?

While scientific breakthroughs improve the lives of patients, they also can richly reward the drug’s creators, note the analysts at Evaluate Pharma (2). Recent successes and the implementation of the US tax cuts may spur renewed investment and acquisitions in 2018. The drug therapy successes need to continue, however, to keep investors interested in the market. The bar for success is set high with rapid progress during the past few years, Evaluate Pharma reports, and disappointments would remind investors that, in biopharma, “failure is a fact of life.”
A SOLUTION TO PHARMA’S PRICING PROBLEM?

While lower tax bills may help fill biopharma company coffers, the debate over the high cost of prescription drugs remains a threat to profitability. A 2017 survey (6) by PwC’s Health Research Institute found that, in general, bio/pharma executives recognize that the industry has a drug pricing problem. Executives are split, however, as to how—or if—the problem should be addressed.

The survey assessed opinions of executives from pharma and insurance companies on drug prices and value-based payment models; 45% of the respondents expect the Trump administration to accelerate downward pressure on drug prices. More than half of the respondents (54%) thought new federal or state drug pricing laws were very or somewhat likely to be enacted.

Respondents were equally split (44% responding “yes,” 44% responding “no”) on the question: Do you think the industry should consider limiting the growth of drug prices during the next fiscal year? However, more than half (53%) said their organization was not considering limiting the growth of drug prices during the next fiscal year; only 23% said their organization was considering limits to growth of drug prices.

The PwC report explored the potential of value-based contracts: a drug’s price is set based on how it performs in real-world settings versus the current approach of basing pricing on data collected during controlled clinical trials. Successful therapies would create rewards; drugs that did not perform may result in reimbursements to patients.

Pharma and health industry executives surveyed expressed enthusiasm for value-based contracts; however, participation is limited. Only one-quarter of the surveyed pharma executives reported that their organizations had participated in a value-based program; however, 80% of those that participated said the contracts were successful. More than one-third (38%) said the potential rewards of a value-based contract were worth the risks.

Value-based pricing models face a number of operational hurdles, including the lack of measurable outcomes regulatory questions, data sharing, and establishing agreement on performance metrics. The value for the patient must also be assessed.

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6. PwC, Launching to Value: Pharma’s Quest to Align Drug Prices with Outcomes, September 2017. 

Gottlieb Outlines FDA Policy Goals for 2018

Reducing the number of regulations was a key component of the Trump administration’s 2017 agenda. FDA Commissioner Scott Gottlieb (1) noted the agency must recognize “when scientific innovations warrant new, more flexible regulatory approaches in order to make sure advances in care can reach patients.” To accomplish this, he wrote, the agency must “continually adapt our regulations to enhance efficiency, improve our effectiveness, and update old and out-of-date requirements.”

Planned 2018 regulations for drug compounding facilities would clarify which drugs may be compounded and promote more efficient, streamlined manufacturing standards, while ensuring safety and quality measures. Another proposed rule would establish national standards for the licensing of prescription drug wholesale distributors and third-party logistics providers, as part of track-and-trace requirements.

Clearly defined standards must not place unnecessary burdens on regulated companies, Gottlieb wrote, and should reflect the latest science. Outdated rules will be removed, he noted, singling out “an outdated inspection provision for biologics and outdated drug sterilization requirements to remove barriers to the use of certain sterilization techniques.”

The agency also faces 2018 deadlines associated with the 21st Century Cures Act including drafting guidance documents for patient-focused drug development; reporting to Congress on standards for advanced regenerative therapies, compliance activities, and hiring authority or scientific, technical, and professional personnel; and holding public meetings on the qualification of drug development tools.

A key deadline—Nov. 26, 2018—looms for bio/pharma companies to comply with requirements for product identifiers and verification in accordance with the US Drug Supply Chain Security Act.

Reference

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The small number of new drug approvals in 2016, only 22 (1), may have been an anomaly. As of Nov. 14, 2017, FDA’s Center for Drug Evaluation and Research (CDER) approved 38 new drugs in 2017 (2) and was on track to achieve numbers similar to the 41 approvals in 2014 (3) and 45 approvals in 2015 (4). The approved drugs include a number of firsts in drugs for untreated diseases and new modes of action. Nearly two-thirds were approved under one or more accelerated pathways and just over one-third were designated as orphan drugs.

HEALTHY MARKET FOR APIs

Given the return to record-level FDA approvals, it is not surprising that most industry analysts predict strong growth in the market for APIs. Markets and Markets, for instance, predicts the global API market, including chemical and biologic branded and generic-drug substances, will expand at a compound annual growth rate of 6.3% from $157.95 billion in 2016 to $213.97 billion in 2021 (5). Market research firm Grand View Research predicts the value of the global API market will reach $239.8 billion by 2025 (6).

Growth is attributed to an aging population with a concomitant rise in age-related diseases and an increase in lifestyle-induced conditions and cancer. Small-molecule APIs account for the greatest share of the market (6), which reflects the rate of approvals for drugs based on chemical and biologic APIs; in 2017 nearly 75% of the approved drugs...
as of November 14 were formulated with small-molecule APIs (2). Captive manufacturers held the greatest market share, but due to increased outsourcing of API manufacturing, contract manufacturers are expected to expand their share more rapidly in the coming years. Demand for generic APIs is also increasing rapidly (6).

**BIOLOGIC-BASED DRUGS AND GENE THERAPIES**

Nearly one-quarter of the drugs approved by CDER were biologic-based drugs (Table I). Although not approved by CDER and thus not appearing on its list of novel approved drugs (2), FDA, through the Center for Biologics Evaluation and Research, has approved gene therapies for the first time in 2017.

The first, Kymriah (tisagenlecleucel) from Novartis, was approved in August and is a chimeric antigen receptor (CAR) T-cell immunotherapy for the treatment of patients up to age 25 years with B-cell precursor acute lymphoblastic leukemia (7). Kymriah was approved under Priority Review with the Breakthrough Therapy designation. At the same time, FDA expanded the approval of Actemra (tocilizumab) from Genentech for the treatment of patients two years of age or older with cytokine release syndrome that occurs with CAR T-cell therapy. Because of the risk of cytokine release syndrome (CRS) and neurological events, Kymriah is being approved with a risk evaluation and mitigation strategy (REMS), which includes elements to assure safe use (ETASU). FDA is requiring that hospitals and their associated clinics that dispense Kymriah be specially certified and trained to recognize and manage CRS and neurological events.

**Table I:** FDA new drug approvals as of Nov. 30, 2017. Source: FDA.
The second, Yescarta (axicabtagene ciloleucel), is also a CAR T-cell therapy, but for the treatment of adult patients with certain types of large B-cell lymphoma who have not responded to or who have relapsed after at least two other kinds of treatment (8). Yescarta was approved under Priority Review and had both Breakthrough Therapy and Orphan Drug designations. Yecarta was approved with a similar REMS.

MANY ACCELERATED APPROVALS

Manufacturers continue to leverage the four expedited review and approval programs—Fast Track and Breakthrough Therapy Designations and Accelerated Approval and Priority Review processes—made possible with passage of the FDA Safety and Innovation Act (FDASIA) in 2012. FDA, under Commissioner Scott Gottlieb, is also committed to accelerating the approval of new drugs (9). Nearly two-thirds (24 out of 38, 63.2%) of the drugs approved in 2017 through mid-November were filed under at least one of these four programs. Of those 24 drugs, just over one-third qualified for two programs, and nearly 16% for three. Of the four programs, 22 drugs were approved under Priority Review, 14 as Breakthrough Therapies, eight with the Fast Track designation, and six with Accelerated Approval.

MORE ORPHAN DRUGS

The Orphan Drug Act (ODA) was passed in January 1983 to encourage the development of drugs to treat rare diseases. Drugs intended to prevent, treat, or diagnose a disease/condition that occurs in less than 200,000 patients in the United States may be designated as an orphan drug. Developers also can receive tax credits for clinical research expenses and seven years of marketing exclusivity upon FDA approval.

In the 10 years prior to passage of the ODA, the pharma industry commercialized only 10 products for rare diseases; since 1983, more than 450 orphan drug products have been approved for more than 600 indications (10). In addition, 60% of the 87 Breakthrough Therapies approved from January 2013 to Sept. 15, 2017 are indicated for rare diseases and accounted for 25% of the orphan drug approvals. Nearly 75% of orphan drugs received Priority Review. In 2017, 13 of the 38 new drugs approved through November 14, or 34%, were classified as orphan drugs.

LOTS OF GENERIC APPROVALS, TOO

FDA approved a record number of abbreviated new drug applications (ANDAs)—763 approvals and 174 tentative approvals—in fiscal year 2017 (11), compared with 639 ANDA approvals and 183 tentative approvals in fiscal year 2016 (12). Not only were more ANDAs approved in 2017 compared to 2016, a much higher number of ANDAs was received as well.

In addition, as of Nov. 28, 2017, FDA had approved 65 first generics (13)—or products that are the first generic competitors to their branded counterparts—and looks to be on track to meet or exceed last year’s figure of 73. The increased rate of approvals is attributed to an increase in FDA personnel by nearly 1000 as a result of funds collected through the Generic Drug User Fee Amendments. FDA has also prioritized the approval of generics to help reduce drug costs.

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#PDAANNUAL
Drug Pricing and Quality Are Top Issues for 2018

Concerns that high and rising drug prices hinder patient treatment will continue to shape pharmaceutical markets in what promises to be a tumultuous year in Washington. Policy makers will weigh access to medicines with the desire to encourage biopharmaceutical R&D, which relies on regulatory efforts to streamline clinical research, ensure product quality, and achieve more efficient oversight. The November midterm Congressional elections already are heating up, as Republicans seek to maintain control of the House and Senate amidst continuing debate over government funding and healthcare policies. These developments will affect resources and initiatives for FDA, the National Institutes of Health, and federal and state health programs.

Global regulatory issues will be important, as drug sourcing and production expands overseas and disease outbreaks threaten public health around the world. International harmonization of regulatory standards and mutual recognition agreements will advance as authorities look for efficiencies in ensuring drug quality, in managing product lifecycles, and in blocking illegal trafficking of counterfeit drugs. Drugmakers also face extensive changes under Brexit, including relocation of the European Medicines Agency to Amsterdam and the need to ensure appropriate marketing authorizations in Europe.

Coverage and Controls

The heated, ongoing debate over revising the Affordable Care Act (ACA) and state Medicaid and children’s health programs will remain in the spotlight as manufacturers evaluate how policy changes may limit drug coverage and reimbursement. Pharma companies backed the ACA and agreed to pay millions in additional taxes to expand pharmacy benefits. Now consumers may face higher out-of-pocket costs that will squeeze drug utilization and ignite further efforts to rein in pharmaceutical prices. The Centers for Medicare and Medicaid Services (CMS) recently revised how Medicare Part B pays hospitals for administering certain drugs and seeks to facilitate coverage of newly approved biosimilars and generic drugs. A new proposal calls for Medicare Part D prescription drug plans to share with patients the rebates and discounts negotiated by manufacturers and pharmacy benefit managers (PBMs). This push for more transparency in drug prices and discounts could erode revenues for PBMs and further escalate the finger-pointing by manufacturers, insurers, and PBMs over who’s to blame for high-priced medicines.

These trends will build interest in value-based pricing strategies that link drug reimbursement to patient response to treatment. CMS and insurers also contemplate arrangements that spread reimbursement over several years for important one-time therapies. Manufacturers will need strong data to justify launch prices, especially for targeted therapies. And payers will look more to reports from the Institute for Clinical and Economic Review (ICER) and other third-party analysts on whether benefits of a new medicine justify costs.

Encouraging Innovation

A main concern for the biomedical research community is that any form of price controls would discourage private investment in biomedical innovation and limit development of new cures for critical diseases. Even though drug companies

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enjoy healthy profits, policy makers are reluctant to dampen the current boom in scientific discovery that has led to new gene and cellular therapies and robust R&D pipelines. FDA approved more than 40 novel medicines through early December 2017, heading for a record year.

US-patent policy and market exclusivity provisions are crucial to maintaining an inviting climate for investing in the biotech industry, but issues have emerged about innovator firms using patents to block competition. The development and marketing of new biosimilars face delays from intense patent battles, and a recent effort to extend protections by transferring patents to a Native American tribe has generated a strong backlash. These actions fuel questions about overextended exclusivity periods for newly approved drugs and biologics, particularly for orphan drugs and reformulated products. The Supreme Court will weigh related issues as it considers an important case in 2018 that could revise the current US Patent Office process for reviewing patent challenges.

While FDA generally avoids involvement in pricing issues, commissioner Scott Gottlieb looks to enhance consumer access to medicines by promoting market competition. A main strategy is to speed the development and approval of generic drugs, particularly for complex therapies and combination products and in classes dominated by one or two brands. Gottlieb also wants to prevent brands from blocking generic-drug makers from obtaining supplies needed for bioequivalence testing and other tactics that delay market entry.

More efficient and timely FDA review and approval of new medical products also will enhance competition, and the agency should gain added flexibility in this area from implementing the 21st Century Cures Act and reauthorized user fee programs. Further advances should emerge in the coming months as Gottlieb unveils more proposals for spurring efficient clinical research methods, particularly to broaden indications for cancer therapies, and wider use of digital technology and updated information systems. Janet Woodcock, director of the Center for Drug Evaluation and Research (CDER), is working to further automate and better manage the new drug development and application review system. And Peter Marks, director of the Center for Biologics Evaluation and Research (CBER), is implementing a framework for identifying and evaluating regenerative medicine advanced therapies (RMATs), including gene therapies.

FDA wants manufacturers to update facilities and processes to ensure more reliable production.

To meet goals for the timely evaluation of applications for these cutting-edge medicines, including priority generics, FDA wants manufacturers to update facilities and processes to ensure more reliable production of high-quality medicines so that manufacturing issues will not delay the approval of new breakthrough drugs or biosimilars. To this end, FDA is requiring applications for new drugs, biologics, and generics to list all facilities involved in product testing and production in order to meet accelerated review goals. Ongoing shortages in sterile injectibles, biotech therapies, and even conventional drugs spotlight the need for industry to invest in modern facilities and quality operations able to detect and prevent distribution of adulterated and contaminated medicines.

COMBATING OPIOIDS

The deadly opioid epidemic, which is taking thousands of lives and driving up healthcare costs on every level, presents serious challenges to pharmaceutical companies. Health authorities and medical practitioners recognize the need for pain medicines for patients with genuine need of treatment, while also struggling to curb excessive prescribing and distribution of drugs subject to abuse and misuse. Congress and the White House have rolled out policies and plans for limiting inappropriate opioid use and for expanding treatment for addicts and access to opioid overdose rescue drugs to lower the death rate from abuse and will look to implement new strategies more effectively.

FDA has ramped up its direct involvement in tackling opioid abuse by encouraging research on new non-opioid pain treatments and more effective medicines to prevent and treat addiction. A related goal is to help overcome hurdles in developing low-cost generic abuse deterrent formulations (ADFs) and overdose treatments and to devise more secure packaging and distribution strategies for pain medications.

On the international front, FDA is collaborating with other agencies to combat import of falsified/substandard medicines, including dangerous pain treatments from overseas. At home, opioid manufacturers face criminal investigations and lawsuits for excessive marketing and distribution of these products, and legal challenges are likely to escalate as overdose rates continue to rise.◆
What to Watch for in 2018

Jim Miller

The industry will see an impact from financing, M&As, advanced therapies, generic drugs, and the retail market in the new year.

It was a great year for much of the bio/pharmaceutical contract manufacturing and development (CDMO) industry in 2017. Research organizations continued to generate hundreds of new candidates, while venture capitalists and private equity investors maintained a robust flow of new funding to emerging bio/pharma companies, which are highly dependent on CDMOs. An active deal environment provided rich exits for CDMO founders and investors.

The momentum from 2017 looks like it will continue into 2018, but one should never extrapolate today’s trends inexorably into the future. Here are five industry themes to watch closely for their potential impact on the CDMO industry.

**BIO/PHARMA FINANCING**

The demand for CDMO services has historically been tied to funding cycles for emerging bio/pharma companies, and 2017 was the fifth year of the upward slope of the funding cycle that began in 2013. The capital raised by emerging bio/pharma in 2017 should certainly maintain demand for CDMO services through 2018. Indeed, new business bookings by clinical contract research organizations (CROs), a bellwether for development activity, remained quite strong through 2017.

CDMO executives should keep a close eye on the fundraising environment, especially the public equity markets.

**MERGERS AND ACQUISITIONS**

There were some very large deals in the CDMO industry in 2017, and a lot of smaller ones. Private equity firms continue to be drawn by the high level of drug development activity and the opportunity to roll up small CDMOs into larger entities. Larger CDMOs continue to pursue strategic acquisitions that add technical capabilities and provide entry into new market segments.

The industry will see more M&A activity in 2018, but the pace may slow down. Valuations have gotten quite high, even for smaller properties that require investors to fund substantial additional capital for capacity expansions and upgrades. Financing will get progressively more expensive as interest rates rise during the year; that could force valuations down but potential sellers may balk at taking lower valuations than their competitors got just a few months ago.

One development to watch for is a very big deal involving an industry leader, along the lines of Thermo Fisher’s acquisition of Patheon and Lonza’s acquisition of Capsugel in

2017. The largest CDMOs need to do deals to deliver on promises to investors and to increase their ability to service global bio/pharma companies with their billions in manufacturing and R&D expenditures. It would not be surprising to see another large private equity firm or strategic buyer from outside the industry make a game-changing entry into the CDMO industry.

ADVANCED THERAPIES

New treatment modalities such as gene therapy, cell therapy, and antibody drug conjugates are becoming a bigger part of the new drug pipeline. Most of the candidates are early stage, with a high percentage still owned by academic institutions, but some initial clinical successes in actually curing once-incurable diseases is stoking investor interest, and established bio/pharma companies are actively buying up advanced-therapy companies.

Advanced therapies present a challenge for CDMOs because their business model and technology often don’t fit the traditional CDMO model. Many of the candidates are autologous (i.e., they involve taking cells from a patient, processing them with the sponsor’s technology, and re-injecting them into the same patient). That is very different from the CDMO model of producing multiple units of a single product.

Still, a number of entrepreneurial CDMOs have positioned themselves for advanced therapies, and several established CDMOs have built positions that are expanding with acquisitions and internal investment. Demand for these services appears strong, and the industry can expect to see further M&A activity in this sector during the year, as major CDMOs look to add advanced therapies to their portfolios.

RESTRICTURING IN GENERIC-DRUG INDUSTRY

Pricing and margins for generic drugs continue to spiral downward, and regulators and payers are determined to keep the pressure on. In the US, the FDA commissioner has promised new procedures and regulations to speed approval of generic drugs, and the nominee to head the Department of Health and Human Services has promised to focus on bringing drug prices down. In Europe, the turn from branded to commodity generics has undermined the industry’s profitability as governments use tendering to purchase pharmaceuticals.

CMOs will do well to follow developments in the retail supply chain, because they could create new opportunities and challenges.

The pressure on generics has significant implications for the bio/pharma CMO industry. Much of the industry has been dependent on branded generics, especially the European CMOs. Lost volumes and narrowed margins, compounded by overcapacity in solid dose manufacturing, are forcing CMOs to restructure, including facility shutdowns.

The problem could be compounded by the restructuring efforts of the large generic-drug companies themselves. Some, like Teva, are committed to downsizing their sprawling and inefficient manufacturing networks. Others, like Sandoz, are reportedly preparing to exit the solid dose portion of their business, which is also likely to result in plant closings. The risk to CMOs is that some of the closed or divested manufacturing facilities will end up becoming CMO operations themselves, worsening the overcapacity problem.

RETAIL REVOLUTION

CMOs will do well to follow developments in the retail supply chain, because they could create new opportunities and challenges. The pharmaceutical industry was rocked at the end of 2017 when the retail and mail order pharmacy giant CVS announced that it intended to buy health insurer Aetna. If the deal were to go through, it could drive a lot of changes in the healthcare delivery system, concentrating more market power in the hands of a few large integrated providers.

The CVS–Aetna announcement came in the midst of speculation that Amazon is preparing to enter the drug distribution business. The online retailing giant threatens to disrupt the way patients get their drugs today thanks to its large customer base, skill in app-based ordering, warehousing and distribution scale, and willingness to take low profit margins.

The kind of market power that might be accumulated by CVS/Aetna and Amazon could create new demands on drug sponsors and manufacturers over issues such as price, inventory maintenance, just-in-time delivery, and packaging. CMO executives should probably devote some time to understanding the implications of those downstream changes and begin thinking about how they should respond.
Expansions in Cell Culture Facility Offerings

Feliza Mirasol

Recent investments show expansion activity in cell culture facilities.

The upstream cell culture sector has seen expansion activity recently as some contract biomanufacturers invest in their cell culture facilities. Major projects announced in the past year include Lonza’s new Ibex solutions that the company is building in Visp, Switzerland, to support multiple technologies, including monoclonal antibody (mAb) cell culture, and FUJIFILM Diosynth Biotechnologies’ new cell culture laboratories in Teesside, UK, among others.

**LONZA INVESTMENT IN MODULAR FACILITY**

Lonza is building Ibex, a complex of five modular buildings providing 100,000 m² of surface area. Construction began in June 2017. The first two buildings are due to be finished and ready for outfitting by mid-2018 and expected to be fully operational by 2020. In addition to Ibex, Lonza has previously built and licensed mammalian facilities in the United States, United Kingdom, Spain, and Singapore (1).

Ibex solutions is a new biological development and manufacturing concept that couples flexibility in facility build-out with tailored business models leveraging the company’s expertise and service network in Visp, according to Marc Funk, COO, Lonza Pharma & Biotech.

“Ibex biomanufacturing comprises a modular, technology-independent development and manufacturing complex that is capable of supporting...”
activities across multiple technologies, including mammalian, microbial, cellular, and bio-conjugate, from late drug discovery to manufacture,” Funk says. The complex will be able to operate at capacities varying from single-use to large scale, depending on customer requirements, according to Funk.

In addition to infrastructure and know-how, Ibex offers flexible models to match and adapt to individual customers’ expectations and forecasts, according to Funk. The availability of a modular complex with pre-built shells means time-to-market can be reduced by 12 months or more, he asserts.

One of the two initially finished buildings at the new complex will be occupied by Sanofi, Funk says. This move is in line with a joint venture that Sanofi and Lonza entered into in February 2017. The two companies are jointly investing approximately CHF290 million (US$298 million), split equally between them, for the joint venture (2). The second of the two buildings will house a mix of customer-dedicated suites and have capacity for polysuites.

**FUJIFILM CELL CULTURE LABORATORY EXPANSION**

In the third quarter of 2017, FUJIFILM Diosynth Biotechnologies, a biologics contract development and manufacturing organization (BioCDMO), opened 10,000 ft² of newly built cell-culture process development laboratories in Wilton Centre, Teesside, UK. The laboratories were built through a JPY 12-billion (US$125-million) investment announced by the BioCDMO’s parent company, FUJIFILM Corporation, in April 2017 (3).

The Wilton facility is located close to the company’s site in Billingham, UK, which allows for easy access to both facilities.

“There is great scientific talent in the Northeast of England which is a perfect synergy with the Process Development expertise that we have been developing over the past 25 years,” says Funk. “We are excited to be part of a growing industry and the part we play in growing our industry.”

The availability of a modular complex with pre-built shells can reduce time-to-market by 12 months or more.

Although the BioCDMO says it has intention to invest further in growing its process development capabilities, it has no concrete new investment plans at present.

The new laboratories are dedicated to supporting activities in the company’s Saturn mAb Platform, which is designed to enable rapid access to process development and manufacturing capacity.

“The foundation of FUJIFILM Diosynth’s Saturn mAb Platform was built on its 25+ years of analytical and process development and manufacturing experience. The platform has built-in best practices, from our Apollo expression system to the latest high throughput process development technologies for process development,” Funk says.

“The platform is adaptable to the customer’s existing cell lines as well. Once the platform has been proven to work for a customer’s monoclonal antibody, FDB [FUJIFILM Diosynth Biotechnologies] de-risks the production as we will guarantee performance,” he adds.

“From a GMP [good manufacturing practice] perspective, the Saturn mAb Platform offers a dedicated high-capacity mAb-only manufacturing facility with a simplified off-the-shelf supply chain and batch documentation,” Funk explains.

In addition to the Wilton facility, FUJIFILM Corporation’s overall JPY 12-billion (US$125-million) investment includes an expansion in the US at its site in Texas. The company completed a JPY 10-billion (US$89-million) cGMP production facility in April 2017 for its FUJIFILM Diosynth Biotechnologies Texas (FDBT) unit.

This facility was built in part with funding from the Biomedical Advanced Research and Development Authority, an office of the US Department of Health and Human Services. FUJIFILM plans to invest an additional JPY 3 billion (US$27 million) to outfit the Texas facility with mammalian cell-culture bioreactors (4).

The FDBT facility is scheduled to start operation in 2018 and will be the manufacturing center of excellence for the Saturn mAb Platform. It will have an initial cell-culture capacity of 6000 L via three 2000-L bioreactors. The facility is designed to allow for future expansion that can accommodate up to 24,000 L of upstream capacity to meet clinical and commercial demands.

FDBT was acquired by FUJIFILM in 2014 through its FUJIFILM Diosynth Biotechnologies USA subsidiary.
and became a wholly owned subsidiary in March 2017.

OTHER CELL CULTURE INVESTMENTS

In addition to Lonza and FUJIFILM, Sartorius Stedim Cellca, a part of Sartorius Stedim Biotech, also recently announced an investment in a new cell culture facility.

In September 2017, the company started construction on a new EUR 30-million (US$36-million) Cell Culture Technology Center in Eselberg, Germany, which is scheduled to be completed by the end of 2019. The location of the new facility places it in the northwestern scientific hub headquartered in Ulm, Germany (5).

The company has thus far been operating in a rented building in Laupheim, Germany. The new facility will approximately double the company’s space, and the new location will provide closer proximity to universities and research institutes in Ulm’s Science Park, according to the company.

The company purchased the property, which spans more than 6000 m², at Science Park III in Eselberg in November 2016. The Cell Culture Technology Center can be expanded by a further 5000 m² as needed, according to the company.

Sartorius Stedim Cellca, which develops cell lines and protein production processes, licenses technologies for the production of proteins, and offers cell culture media, currently employs around 90 people. The company intends to expand its workforce to more than 120 people over the medium term (5).

Further investment in cell culture capabilities includes pharma major Novartis. In August 2016, Jacobs Engineering Group, a provider of technical, professional, and construction services, was awarded a $100-million contract to expand Novartis’ biotechnology center in Huningue, France. The expansion project is scheduled to be completed by 2020 and adds cell-culture bioreactors to the site (6).

Jacobs is providing engineering, procurement, and construction management services and will increase the site’s production capacity by 70%.

In addition, it will create a second line of purification that allows for multiple drugs to be manufactured simultaneously. At 35,000 m², Novartis’ Huningue site houses one of the largest production facilities for mAbs produced from mammalian cells (6).

Another expansion move involves Sumitomo Dainippon Pharma, an Osaka, Japan-based pharmaceutical company, which boosted its cell-culture production capabilities.

In April 2017, the company formed a deal with Hitachi, a Japanese business solutions provider, to supply automated cell mass-culture equipment for regenerative medicine using human induced pluripotent stem (iPS) cells (7).

The equipment supplied supports Sumitomo’s research into making practical use of dopaminergic neural progenitor cells. The equipment consists of single-use consumables, such as bottles, tubes, and cell culture dishes.

Further investment in cell culture capabilities includes pharma major Novartis.

The iPS cells can be cultured and differentiated efficiently because they can be manufactured in large amounts automatically and be observed under closed sterile environment, according to Hitachi (7).

In addition to supplying the equipment, Hitachi has formed a joint research deal with Sumitomo to evaluate the validity of processing methods that will be adjusted for practical use of the automated cell culture equipment.

The companies aim to use the equipment for the clinical treatment of patients with Parkinson’s disease with human iPS cells. iPS cells have the ability to be developed into different types of tissues and organs and can be potentially used as regenerative medicine to repair wounded cells.

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Evolving UF/DF Capabilities

Cynthia A. Challener

Advances in TFF and single-use systems help advance UF/DF on the continuous processing path.

Ultrafiltration/diafiltration is a core downstream bioprocessing technology that continues to evolve. “Batch ultrafiltration/diafiltration (UF/DF) is a very economical, high yield, and robust separation process based on size exclusion that finds application for a wide range of biotherapeutics,” notes Andrew Bulpin, head of process solutions for MilliporeSigma. UF involves separation of components on the basis of molecular weight/size. It is a pressure-driven process in which soluble macromolecules (e.g., proteins as products) are retained while small molecular-weight particles (e.g., salts, amino acids, mono- or disaccharides), and fluid/water pass through the membrane as waste, according to Mayank Dadhwal, filtration global product manager at GE Healthcare Life Sciences. DF is used to exchange buffer solutions.

Batch UF/DF is used in nearly every biotherapeutic process for final formulation, notes Bulpin. DF is used to exchange the buffer to one that is preferred for storage stability and ease of administration; UF is employed to concentrate the therapeutic to its final formulation concentration. For high-concentration products intended for administration via subcutaneous injection, UF/DF studies are often conducted to understand the relevant viscosity limitation and determine the maximum concentration that can be achieved, according to Marc Jenke, senior product manager for crossflow filtration systems at Sartorius Stedim Biotech.

UF/DF is also used in some cases for buffer exchange and bioprocess fluid concentration prior to or in between different chromatography steps during downstream processing. Vaccine purification using batch UF/DF allows retention of the cell, virus, or glycoprotein vaccine by the UF membrane, while smaller impurities pass through the membrane. In addition, batch
UF/DF is used to remove unreacted reagents from therapeutic conjugates such as antibody-drug conjugates (ADCs), PEGylated proteins, carbohydrate conjugates, and others.

For instance, biopharmaceutical contract development and manufacturing organization CMC Biologics typically uses UF/DF for final buffer exchange and concentration, according to Magnus Schoeder, director of downstream process development with the company. On occasion, UF/DF is used to concentrate clarified harvest material or as an intermediate buffer exchange step prior to the final buffer after diafiltration, according to Jenke. “These systems are easy to use and are available for both development and commercial production, allowing straightforward transfer of processes from one department to the other. In addition, there are established service and training concepts, operators know exactly what to do, and release of final product is facilitated because quality personnel can properly interpret the data,” he explains.

TFF systems for UF/DF can be either stainless-steel or single-use and are typically configured with hollow fibers or cassettes. “As the biopharmaceutical market expands, the need for greater facility utilization increases because multiple drugs must be released to the market with very short turnaround times. UF/DF system design is therefore crucial to facility fit for both multi-product and single-product facilities,” observes Dadhwal. It can be difficult to design a one-size-fits-all UF/DF system, however, given that a wide range of process titers and drug substance concentrations are processed in multiproduct facilities.

Employing two stainless-steel UF/DF systems to achieve high drug substance concentrations can significantly increase both cost and process complexity, he adds. “Automated single-use TFF systems with disposable flowpaths and reduced hold-up volumes that can be used with highly concentrated fluids not only increase facility flexibility, they help minimize the risk for cross-contamination and allow faster changeover times due to reduced need for cleaning and greater process consistency due to reduction in the opportunities for operator error,” Dadhwal says.

CMC Biologics uses plate and frame systems with various pumps, load cells, online detectors, and control loops, either in the form of conventional clean-in-place/steam-in-place capable skids or single-use setups with disposable product flowpaths, according to Schoeder. Technologies other than crossflow filtration are used in some cases for UF/DF processes. At the bench scale, for instance, size-exclusion chromatography (SEC) is commonly used to achieve size-based separations, according to Bulpin. It is impractical for larger-scale processes, however, because it requires dilute protein concentrations and low flow rates. Bulpin adds that crystallization and freeze-drying have been applied for concentration, but they tend to be more expensive, less widely applicable, and require extensive development. Large-scale countercurrent dialysis is possible for very sensitive molecules, according to Schoeder, but has limitations around scalability and is not frequently used.

One alternative that is gaining attention for high-concentration formulations is single-pass TFF (SPTFF). It can relieve the working volume constraints of conventional systems, according to Dadhwal, but is an emerging concept. As a result, conventional TFF systems are still the most accepted solutions for UF/DF applications.

**CHALLENGES OF CHANGING FEED STREAMS**

Changes in upstream production processes have led to higher titers and increased batch sizes for UF/DF processes. Final formulations with higher concentration targets are now preferred because they allow for ease of administration. These changes have led to the need for larger UF/DF systems and closer attention paid to scale-up issues such as mixing, pumping damage, and holdup volumes, according to Bulpin. “Higher final concentrations have also led to a greater understanding of solute partitioning such as Donnan exclusion, where charged excipients interact with higher concentrations of charged therapeutic products to alter the final buffer after diafiltration,” he notes.
Growing interest in more potent molecules such as ADCs has also had an impact. “For these biomolecules, avoiding exposure to operators and minimizing liquid waste are important,” Dadhwal comments. In addition, crossflow filtration solutions for biocongjugates must also be compatible with various chemicals, including solvents, according to Jenke. “Development of UF/DF production systems with materials that provide the necessary separation/concentration performance while also being compatible with various chemicals has been a focus at Sartorius Stedim Biotech,” he remarks.

Overall, there has been increasing interest in implementation of single-use TFF systems for UF/DF. Similarly, Dadhwal notes that cell- and gene-therapies, which are entering the commercialization stage, benefit from single-use UF/DF systems because they are produced on a much smaller scale than blockbuster monoclonal antibodies. These therapies also may have requirements such as sterility of the liquid path due to the size of the virus or yield concerns when viruses are sterile filtered. “In both cases, completely closed operation can be achieved with single-use systems,” he says.

At CMC Biologics, one challenge has been the need to balance product quality, processing time, facility fit, and product recovery for high-concentration (200 g/L and higher) formulations for subcutaneous applications. New challenges, according to Schoeder, include higher viscosity solutions with less-efficient mass-transfer and mixing challenges, designing manufacturing systems that allow for processing of high initial volumes/high fluxes and yield low volumes/low fluxes at the end, with subsequent low dead-volume product recovery.

Solutions for Evolving Needs
These challenges have led to advances in TFF technology for UF/DF applications. In particular, the introduction of increasingly sophisticated single-use solutions has had a significant impact, according to Dadhwal. “Novel TFF membranes with modified channel geometries and screen designs for improved handling of high-viscosity scenarios have been appreciated at CMC Biologics,” says Schoeder. These new modules optimize the design and manufacture of the feed screen channel to enable high back-transport of solutes from the membrane while also reducing the pressure drop along the feed channel, according to Bulpin.

Schoeder adds that the introduction of variable path-length, flow-through detectors for online monitoring of concentration throughout the entire process has also been important for improving UF/DF performance.

Bulpin sees SPTFF as an important advance that is enabling continuous concentration of larger batch sizes. “While batch systems require repeated passes of the biotherapeutic solution through filter assemblies to achieve a target final concentration, SPTFF operates existing filters in a different configuration to achieve target concentrations continuously in one pass. They can also be employed at various stages of a process to eliminate tank bottlenecks and improve the efficiencies of other unit operations,” he explains.

The rapid growth of highly potent ADCs has also challenged UF/DF system manufacturers to develop self-contained, holderless filter capsules that can be operated in a closed system to minimize operator exposure, according to Bulpin. “These pre-sterilized capsules are convenient for plug-and-play operation to improve the throughput in pilot plants and clinical manufacturing operations,” he notes.

Sartorius Stedim Biotech has focused the development of multi-parallel, small-scale crossflow filtration systems with the potential to decrease the hurdles when going from upstream to downstream processing, according to Jenke. The company has a new high-throughput TFF system for parallel screening that can be used for the development of both upstream and downstream (e.g., UF/DF) processes that it will be bringing to market in the near future. The automated system consists of a 10-m² membrane with a 5-mL recirculating volume and up to 16 crossflow channels, allowing the use of small process volumes and speeding up R&D efforts. “Each channel represents a fully equipped and automated crossflow solution. This new system is ideal for process optimization, screening of agents with a relevance for upstream and downstream development, target selection, and determination of optimal buffer type and pH and conductivity values, and more,” Jenke asserts. “It also enables critical experiments to be performed earlier in product development.”

New Manufacturing Paradigms
Continuous processing is of great interest because it enables removal of intermediate tanks, increases productivity, and improves product quality, according to Bulpin. “Continuous processing is the new evolving concept in biomanufacturing, so shaping UF/DF systems to adapt to the continuous manufacturing scenario is the new challenge to be addressed,” asserts Dadhwal. He notes that automation of UF/DF processes is the answer, both at the R&D stage for optimized processes developed using a quality-by-design approach and at the pilot plant and commercial production stages combined with single-use technology for facilitation of continuous operations and effective process monitoring and data acquisition.

Specific examples of equipment that can enable continuous UF/DF processes include sterile UF capsules, which according to Bulpin, aid continuous UF by facilitating easy assembly of closed systems for extended bioburden-free processing times.
Beyond continuous processing, a key ongoing trend in the biopharmaceutical industry is the need to increase operational efficiency and lower the cost of manufacturing. One approach, according to Dadhwal, is to perform processes in controlled, non-classified spaces. “Taking this approach results in the need for more closed operations. In these instances, single-use technology provides an advantage with the possibility to use aseptic connectors and easily avoid bioburden issues with gamma-irradiated tubing assemblies,” he observes.

In addition to more single-use alternatives for UF/DF, Schoeder expects going forward that there will be increasing demand for more SPTFF solutions, including single-pass diafiltration membranes. Other areas with needed improvement include enhanced pilot- and production-scale UF/DF skids and improved automated process development and characterization systems for high-concentration formulation products.

There is also an ongoing need for new UF/DF filters with different pore size ratings, new materials of construction, new designs, and new ways of operating to achieve target separations for new applications, according to Bulpin. New processes can also require tighter filter specifications.

The use of design-of-experiment approaches and data analysis will play an important role in development of downstream manufacturing processes in the near future, according to Jenke. “There is only limited data currently available for UF/DF processes, despite the fact that it can have an impact on molecular stability and overall process efficiency. We see significant opportunity for future developments to improve the manufacturability of this essential downstream process by providing technology that is readily scalable and generates data that are readily analyzed,” he explains.

WuXi Biologics Open Facility in China
WuXi Biologics announced on Dec. 6, 2017 that its new 30,000-L cGMP biologics manufacturing facility in Wuxi, China is operational (1). The company announced a $150-million investment to build the facility in April 2015.

The first phase of construction, completed in September 2016, included two 1000-L disposable bioreactors for perfusion processes. Following the completion of the first phase of construction, the company began a cGMP campaign 15 months later, resulting in the facility being equipped with additional 14 2000-L disposable bioreactors for fed-batch cell culture.

The new 500,000-sq.-ft facility quintuples the company’s existing manufacturing capability. The design had a lower capital expenditure and shorter facility timeline compared to that of traditional biologics commercial manufacturing facilities, the company reports.

EMA Approves Samsung BioLogics Facility
On Dec. 13, 2017, Samsung BioLogics announced that it received approval from the European Medicines Agency (EMA) for the production of a monoclonal antibody (mAb) drug substance at its second facility in Songdo, Incheon, South Korea (2). This marks the first mAb that will be produced at the 152,000-L bioproduction facility, according to the company.

This approval follows the facility’s October 2017 FDA approval for mAb manufacturing. Both EMA and FDA inspections occurred in July 2016.

SGS Adds Sanger Sequencing
SGS has introduced a Sanger sequencing service at its Glasgow, United Kingdom, laboratory to support genetic stability testing and perform identity testing on cell banks, plasmids, and viral seeds/vectors (3). The service is now available under good manufacturing practice (GMP) conditions to clients from December 2017.

Applications include cell bank characterization, virus seed and plasmid identity testing, and genetic stability testing of cell banks. The new service is supported by an investment in ABI Life Technologies’ validated 3500xl DNA sequencing technology and will complement existing services for this testing, to provide comprehensive analysis and characterization solutions for clients involved in the production and manufacturing of biopharmaceutical products.

References

—The Editors of BioPharm International
The heart of any peristatic pump is the tubing. It is the primary fluid-contacting part and is occluded by the pump rotor and housing, thus providing the pumping action. With some attention when installing or changing tubing and proper tubing material selection, the pumping system can be optimized.

**TUBING INSTALLATION**

Proper tube loading can improve the tubing life and overall pumping performance and accuracy. It can also provide consistency between tubing changes by implementing a standardized process for tubing installation.

**Match the pump to the tubing size**

Peristaltic pumps require specific tubing sizes—determined by the inside diameter (ID), the outside diameter (OD), and the wall thickness—to operate correctly. Using the wrong size in a pump can lead to improper function of the retaining mechanism, no pumping action, and even premature failure of the tubing. Use of precision peristaltic pump tubing in the right size can ensure that the pump system will operate correctly.

**Follow the natural curvature**

During manufacturing of the tubing, it is laid up in a coil, which imparts a natural curvature to the tubing. When loading the tubing into a pump, allowing it to follow its natural curvature with the curvature of the occlusion bed will improve tubing performance. If the tubing is twisted, it can roll to one side of the rotor and may strike the rotor place, thus damaging the tubing.
Stretch the tubing
As the tubing is being loaded, giving it a slight stretch by pulling it gently by hand, as shown in Figure 1, will improve performance. Stretching eliminates the potential for excess bunching of tubing at the discharge side of the pump when starting up, which can cause early failure and decrease accuracy of the pump system. Do not overstretch the tubing, which will change its dimensions and thus affect flow rates.

Center the tubing
When loading tubing, make sure it is in the center of the roller and occlusion bed. If installed off center, or with a twist, it can be driven into the rotor plate, causing damage to the tubing.

Following these simple loading steps can ensure consistent tube loading and serve as a standardized process.

TUBING SELECTION
Proper tubing selection, which is detailed in the following section, will ensure that the tubing matches the requirements for the fluid system design. When choosing the right tubing for an application, there are many factors to consider. To make the process simple, use the acronym STAMP—size, temperature, application, media, and pressure—to help remember each factor.

Size
The ID, OD, and wall thickness of the tube are significant factors in pressure and vacuum ratings and must be considered in the decision. The tolerances are also a concern for optimal operation in peristaltic pumps. The typical tolerance of off-the-shelf nominal tubing can be greater than +/-5%. If this non-precision tubing is used, it can cause problems with volumetric accuracy, suction lift, or pressure; poor tubing life can also be a result.

Understanding the fluid being conveyed can help maximize the efficiency of your project to assist with easier flushing and avoidance of costly leaks.

Temperature
Operating temperature is most often considered due to its importance, but cleaning temperature, ambient temperature, and the overall temperature fluctuation must also be considered. Sudden changes or extreme temperatures can negatively affect performance and cause premature failures. A higher cost material has traditionally been the only option to improve performance in extreme temperatures. With advances in manufacturing capabilities, however, multilayer products are available that can help ease this cost while still meeting the performance expectations.

Application
Understanding the full scope of the application is the most complex portion of the selection process and most often overlooked. Regulatory concerns are always at the top of the list. Understanding what documentation is needed and what special regulations must be
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complied with are important; different compliance concerns may call for different material selection. Tubing materials and formulas can be tested to ensure they comply with the appropriate criteria.

Knowing the dynamics (e.g., flow rate, pressure, or viscosity) of the application will assist with material selection for clarity, durometer (relative hardness), flexural fatigue, abrasion resistance, spallation (the tendency of materials to release particulates due to impact or stress), and particulates (pyrogens). There are materials available to combat each of these concerns individually and multi-layer options to solve a mix of these factors.

**Media**
Knowing the media or fluid being transported and its characteristics, such as extractables level, the tendency for adsorption or absorption of fluid into the tubing material, and the tendency of media to entrap particulates, is necessary to assure high purity. Different chemicals attack various materials at different rates, so understanding all the chemicals that might be used in the tubing will help with proper selection. Cleaning agents are often the most aggressive fluids used; be aware of any chemical reactions which might be caused by cleaning or sterilizing agents. Often overlooked are the ambient chemicals (e.g., solvents) present in the atmosphere, either present in the air surrounding the tubing product or dripping by way of leaks or condensation creation. The effect of these chemicals on the tubing should also be considered. If the fluid is very aggressive, a more resistant material can be used, or multilayer tubing can be selected that assists with barrier protection but is not as costly as tubing made completely from a more resistant material.

Some tubing materials can be produced at tighter tolerances for tighter fitting connections to avoid leak points. Others can be produced with a smoother inner surface for better flushing. Understanding the fluid being conveyed can help maximize the efficiency of your project to assist with easier flushing and avoidance of costly leaks.

**Understanding the full scope of the application is the most complex portion of the selection process and most often overlooked.**

Safety also plays a role with material choice. Some requirements mandate viewing the fluid being conveyed. This means the material must have a sufficient level of clarity to see the fluid path and distinguish if any particulates are present. Other options require identifying marks for various chemicals through the use of colored tubing products or specific marking text. Use of these marks is a growing trend in efforts to further company’s safety improvements.

**Pressure**
Vacuum and positive pressure create stress on any tubing product. Ignoring these factors can create hazardous conditions during product use. Use temperature also has a significant effect on the pressure rating for materials, and proper measures must be taken. Changing the wall thickness can help increase pressure rating, as can reducing the overall OD and ID. If these measures are not an option, multilayer products of various materials can help handle the desired pressure as well as maintain the proper condition in the fluid path.

Pressures created during normal operation are not the only factor when selecting the proper tubing. Cleaning or sterilization cycles can create the most extreme pressure conditions and must be considered during the selection.

**SUMMARY**
The peristaltic pump system can be optimized with proper tubing installation material selection that takes into account the size of the tubing and the temperature, application, media, and pressure of the system. When selecting a tubing product, quality is of the utmost importance. Do not shy away from asking the manufacturer about their quality process, and take a plant tour to see how a product is designed and produced. Should something ever go wrong in the field, a manufacturer should have the supporting quality documentation.

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**Factors for choosing the right peristaltic pump**

Remember STAMP:
- Size
- Temperature
- Application
- Media
- Pressure

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Consistent and controlled chromatography column performance is crucial to ensuring product quality for commercial production of recombinant proteins. One method applied to production-scale chromatography columns is called pulsed-input (salt-plug) testing (1–4). This method is typically used to evaluate a freshly packed column where a chemical tracer (typically salt or base solution) is injected, and an elution peak with a Gaussian (normal) distribution is generated. The height equivalent of a theoretical plate (HETP) and asymmetry factor (Af) can be extracted from the Gaussian curve. However, this method is less practical for ongoing monitoring of production-scale chromatography columns in routine manufacturing operations because it is severely limited in sensitivity, needs installation of auxiliary equipment, and is too cumbersome to carry out on a routine basis and obtain results in a robust way.

Another method called moment analysis (5), first applied to chromatography by Martin and Synge (6), is an alternative column assessment tool to the pulsed-input testing method. The analysis is performed on a chromatography transition, which is a response at the column outlet to a step-change at the column inlet. The derivative of the response curve is a peak-like curve, but not necessarily Gaussian distribution. The HETP and Af can then be calculated based on the derivative curve as described in the materials and methods section in this paper.

The transition is typically a result of buffer change as part of the normal operation recipe, thus no dedicated tracer study is needed, and moment analysis can be performed on the in-
process data during or after each batch, without affecting the normal column operation. Thus, it is more practically applied to production-scale chromatography columns in operation (7, 8).

Larson et al. (7) performed moment analysis to assess more than 300 production-scale chromatography transitions. They found that the non-Gaussian HETP method is much more sensitive in detecting bed integrity breaches compared to the Gaussian HETP method (moment analysis with the assumption of Gaussian distribution).

Because moment analysis is performed on the derivative of the sensor data (typically conductivity), which amplifies the noise in the original data, it often requires extensive signal processing or noise filtering, e.g., change band or moving average filter (7, 8), highly depending on the signal-to-noise ratio of sensor data (as illustrated in Figure 1). There are no established standards or best practices on how data should be pre-processed. Different columns require different signal processing approaches, which would thus lead to different results in HETP and Af.

To address this challenge, a “paper-and-pencil” method, which the authors named direct transition analysis (DTA), was developed to overcome the shortcoming of moment analysis. Two column performance indicators, transition width (TransWidth) and direct asymmetry factor (DirectAf), corresponding to HETP and Af, respectively, are directly extracted from the transition curve without complex signal processing.

The main drive behind this approach is to pave the way for validation, which is a regulatory requirement for commercial manufacturing. The calculation procedure of these two metrics and their applications to production-scale chromatography columns are presented in this paper.

**MATERIALS AND METHODS**

**Chromatography data**

In-process data from production-scale chromatography column operations for recombinant protein productions were used for conducting moment analysis and DTA. The chromatography columns were either bind-elute or flow-through covering various affinity chromatography, hydrophobic interaction chromatography (HIC), and ion exchange chromatography (IEX) columns. Conductivity was chosen as a measure of transition. When switching buffers during normal column operation, a step-change in conductivity was introduced at column inlet, and a transition occurred as a response to the step-change at column outlet. Thus, the post-column conductivity data were collected and used for both analyses.

Typically, the transition was chosen at non-product-related phases with large conductivity differences, preferably before loading to the column. Flow-rate data were also used for integration over time to obtain column volume (CV) during the transition. A transition curve was obtained by plotting the post-column conductivity data versus CV, instead of time, to eliminate the impact of operation delays on analysis results. Although DTA is functional for lower frequency data (up to 20-second interval), higher frequency (≤ five-second time interval) post-column conductivity and flow-rate data were desired to ensure reliable analyses.

**Moment analysis**

Moment analysis was conducted based on the theories from the transition study on production-scale chromatography data by Larson et al. (7). Two metrics, non-Gaussian HETP and Af, were calculated based on the smoothed derivative of post-column conductivity data versus CV over clearly defined transition phases. The detailed calculation procedure is shown below:

- The volume \( V \) passing through the column was converted from liter to CV.
- Conductivity \( C \) was normalized to 0 (min.) ~1 (max.).
- Normalized conductivity was plotted against CV.
- The CV was obtained when conductivity crosses the 0.5 threshold, \( CV_{mid} \).
- Conductivity data were renormalized between \( CV_{mid} ± 0.35 \) CV as the transition window.
- Normalized conductivity was interpolated to handle large gaps and super clusters.
- The derivative of the conductivity data was taken and the noise was filtered using Baxter-King band pass filter (9).
The non-Gaussian HETP based on statistical moments, $M_i$, and the column bed height, $H$, was calculated using Equation (10):

$$\text{HETP} = \frac{H \times \sigma^2}{\mu^2}$$  \[[\text{Eq.1}]\]

where $\sigma^2 = \frac{M_2}{M_0} - \left(\frac{M_1}{M_0}\right)^2$, $\mu = \frac{M_1}{M_0}$, and $M_i = \int V \left(\frac{dc}{dV}\right) dV$

Af was calculated using Equation 2:

$$Af = \frac{1}{n} \sum_{i=1}^{n} \frac{V_{bi} - V_{max}}{V_{max} - V_{ai}}$$  \[[\text{Eq. 2}]\]

where $V_{max}$ is the value of $V$ corresponding to $(dC/dV)_{max}$, and $V_{bi}$ and $V_{ai}$ are the value of $V$ at $x\%$ of $(dC/dV)_{max}$. $V_{bi} > V_{ai}$. While single threshold of 10% ($n=1$ and $x=10$) was commonly used for moment analysis (e.g., Larson et al.’s work [7]), multiple thresholds ($n=6$ and $x=10$, 20, 30, 40, 50, and 70) were implemented on the noisy manufacturing process data shown in this paper in order to mitigate the risk of single-point failure.

Direct transition analysis (DTA)

A challenge in the moment analysis is that it usually requires extensive signal processing or noise filtering, because the analysis is performed on the derivative of the conductivity data, which aggravates the noise in the original data. For legacy equipment, it is not uncommon that the signal-to-noise ratio of derivative signal is so poor that moment analysis fails to generate reliable results. Because of this, a “paper-and-pencil” approach, DTA, was developed.

Corresponding to HETP and Af in the moment analysis, two metrics from DTA, TransWidth and DirectAf, were extracted directly from the transition curve of post-column conductivity versus CV without extensive signal processing. TransWidth is a direct measure of band broadening of the column, while DirectAf is a direct measure of asymmetry. As a pre-requisite, moment analysis requires a time stamp at the beginning of buffer change. In real-world application, it can be difficult, depending on data historian setup, for the chromatography skid. DTA, however, does not need the precise timing of buffer change. A detailed calculation procedure (illustrated in Figure 2) is shown below:

- The volume passing through the column was converted from liter to CV.
- Conductivity was normalized to 0 (min.) -1 (max.).
- Normalized conductivity was plotted against CV.
- The CV was obtained when conductivity crosses the 0.5 threshold, $CV_{mid}$.
- Conductivity data was renormalized between $CV_{mid} \pm 0.35$ CV as the transition window.

Figure 1. (a) Comparison between Af from moment analysis (7) and DirectAf from direct transition analysis (DTA) calculated over normal campaign runs of an affinity chromatography column where same-column operations were executed consecutively with little or no pause. (b) The derivative of conductivity data versus column volume (CV) with and without noise filtering from one of the campaign runs.
• The CVs when conductivity crosses multiple thresholds were obtained, respectively.
• TransWidth was calculated as the difference between CVs at thresholds of 95% and 5%.
• DirectAf was calculated as the average of all $b_i/a_i$ that were obtained at multiple thresholds as shown in Figure 2.

RESULTS AND DISCUSSION

Comparisons between moment analysis and DTA

Comparisons of results from moment analysis and DTA for production-scale chromatography columns are shown in the following examples. The first example demonstrates the challenge of implementing moment analysis on manufacturing process data due to the noise in sensor data requiring extensive noise filtering.

The advantage of using DTA is that it is much less impacted by noise and requires no special filtering, therefore, it is easier to implement. To fully demonstrate signal noise effects, moment analysis in this example followed Larson et al.’s work (7) using moving average filter to smooth the derivative of conductivity data and only 10% threshold ($n=1$ in Equation 2) to calculate Af.

Figure 1(a) shows the comparison between Af from moment analysis (7) and DirectAf from DTA calculated over several affinity chromatography column runs during normal operations within a campaign where same-column operations were executed.
consecutively with little or no pause. It is seen that the result from DTA showed more consistency than the one from moment analysis (7) under normal operation conditions.

Figure 1(b) shows the derivative of conductivity data versus CV with and without noise filtering from one of the campaign runs illustrating how noise in original conductivity data can be amplified when taking derivative and complex filtering is necessary for moment analysis.

The second example shows the comparison of results from moment analysis and DTA described in the materials and methods section of this paper and further exploration of the relationship between the two sets of metrics from both analyses. All metrics were calculated based on one-year historical data from a HIC column.

Results are compared in Figure 3. HETP and TransWidth have similar trends (though they have different units in terms of processing length or volume), and Af and DirectAf have similar trends as well. There are distinct offsets between the moment analysis and direct analysis, but the main objective of these analyses is to detect the shift in column performance. In real-world application, acceptance criteria could be established using proper statistical rules, instead of focusing on the absolute values.

To further check the relationship between the two sets of metrics, correlations were performed as shown in Figure 3. Results indicate there are strong linear correlations between HETP and TransWidth (coefficient of determination $R^2=0.88$), and between Af and DirectAf ($R^2=0.75$). Therefore, TransWidth and DirectAf could be good substitutes for HETP and Af.

Case study 1: Chromatography column re-qualification
DTA was used to re-qualify production-scale chromatography columns after a facility upgrade required relocation of multiple previously qualified columns. Blank runs (without loading products) were performed after the columns were moved back to the suite. The conductivity and flow-rate
data from those runs were collected and analyzed using DTA to assess the integrity of the column. For each column, the TransWidth and DirectAf were calculated for the blank runs as well as over the life of the current column pack on which acceptance criteria were established. The acceptance criteria, or the single-value pre-

**Figure 4.** TransWidth and DirectAf trends for ion exchange chromatography column runs including the blank run. The dash lines represent the acceptance criteria based on Equation 3. CV is column volume.

**Figure 5.** TransWidth and DirectAf trends during resin life time process validation for an Affinity chromatography column. The solid line represents the mean value and the dash lines represent the +/-3 sigma range. CV is column volume.

**Figure 6.** TransWidth and DirectAf trends for a hydrophobic interaction chromatography column. The dash lines represent the acceptance criteria based on Equation 3. CV is column volume.
diction interval, were calculated as \([LPL, UPL]\) using Equation 3:

\[
[LPL, UPL] = \bar{x} \pm t_{(1-\alpha/2; n-1)} \left( 1 + \frac{1}{n} \right)^{1/2} s
\]

where \(LPL\) and \(UPL\) are the lower and upper prediction limits, respectively, \(\bar{x}\) is the sample mean, \(s\) is the sample standard deviation, \(n\) is the sample size, and \(t_{(1-\alpha/2; n-1)}\) is the two-sided \(t\)-distribution statistic with \(n-1\) degrees of freedom \((\alpha=0.05)\).

During the relocation, one IEX chromatography column experienced physical impact. TransWidth and DirectAf from its blank run were 0.199 and 1.180, respectively. The single-value prediction interval for TransWidth was \([0.202, 0.238]\) and the single-value prediction interval for DirectAf was \([0.913, 1.312]\). As seen in Figure 4, the TransWidth value was outside the interval, and thus failed to meet the acceptance criteria, leading to a column re-packing. Other columns for which the metrics from the blank runs met the criteria were considered re-qualified and were released for production.

Case study 2: Chromatography resin lifetime process validation

DTA was used to support chromatography resin lifetime process validation (PV). TransWidth and DirectAf were chosen as lifetime indicators of the resin bed integrity. Both metrics were calculated for each column cycle and monitored throughout its intended use period. Figure 5 shows TransWidth and DirectAf trends through the resin lifetime PV for an affinity chromatography column. It can be seen that the TransWidth and DirectAf remain consistent among cycles.

Case study 3: Chromatography column routine performance monitoring

DTA is used together with other critical process parameters for monitoring chromatography column performance on a routine basis. For example, atypical UV peaks were observed from the most recent two runs of a HIC column. DTA metrics were used to assess whether the column bed integrity degraded in addition to other potential root causes. As shown in Figure 6, a shift in TransWidth and DirectAf trends was observed where both metrics for the most recent two runs failed to meet the acceptance criteria based on Equation 3. Thus, a decision was made to re-pack the column. Later, it was confirmed that preferential flow characteristics was formed inside the packed resin bed and the start of channel formation was observed during column unpacking.

CONCLUSION

DTA was demonstrated as a reliable and easy-to-implement approach to qualify and monitor the performance of production-scale chromatography columns. The straightforward calculation algorithm without complex signal processing made DTA easy to implement and the results were less affected by the quality of sensor data. Results from DTA compared against the corresponding ones from the conventional moment analysis showed that TransWidth and HETP, and DirectAf and Af, correlated well, respectively. DTA could be a good substitute for moment analysis, or the two could be used simultaneously to enhance the monitoring and control of chromatography operations.

ACKNOWLEDGEMENTS

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REFERENCES

The importance of antibody discovery and engineering for pharmaceutical development has grown significantly over the past two decades. During the past few years, modeling tools for antibody discovery and engineering have been developed, taking advantage of the structural knowledge existing in the protein database (PDB). The number of structures containing an antibody VH-VL motif is approximately 2350 today, compared to 1800 two years ago. However, the antibody repertoire diversity is around 10 billion, and specific maturation extends it to $10^{13}$.

At Roche, a modeling tool is automatically producing high quality models at a very low computational cost. The tool uses an antibody structural database dissected in heavy and light chains, frameworks, and Complement Determining Regions (CDRs) segments that enables novel features in searching templates during modeling. An accurate prediction of the relative VH-VL orientation ensures the model quality. The VH-VL orientation prediction is also used to predict the CDR grafting success during humanization. A technology based on neighborhood search is used to predict the position of side chains; this represents an add-on to the classical homology modeling (sequence-based) approach.

Attend this webcast to learn how to automate the generation of high-quality antibody structure models.

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- Bioinformatics
- Computation chemists
- Molecular technicians

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**Presenters**

*Guy Georges*
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Stability testing is essential for maintaining the integrity and quality of biopharmaceuticals and for assessing an accurate shelf-life. It is an important aspect of quality control and is an important step in evaluating product safety and efficacy. It is also important for examining how critical quality attributes (CQAs) of a drug substance vary with time under different environmental factors.

**DETERMINING THE RIGHT PACKAGING**

Through stability testing, pharmaceutical companies can ensure the most suitable packaging and/or container closure for the storage and distribution of biopharmaceutical products, according to Russell Crothers, supervisor, Sample Control Unit, Alcami.

“With the right storage, appropriate shelf life determined, and distribution methods in place, the quality of active pharmaceutical ingredient (API) and drug products is safeguarded,” Crothers says.

In addition, understanding potential degradation routes in relation to storage environment is an important factor in establishing the CQAs of a pharmaceutical or biopharmaceutical, according to Ashleigh Wake, director, Biological Services, Intertek Pharmaceutical Services.

“Ultimately, this understanding ensures that the optimal quality control strategy is in place to monitor the continued efficacy and safety of any therapeutic,” Wake says.

“Imagine the situation where, in the first instance, the degradation route of...
a molecule had not been assessed through forced or ‘stressed’ studies. Not understanding this pathway could lead to failure in identifying pertinent degradation products [that] impact the safety and/or efficacy of the product and thus need to be controlled during product release,” says Wake.

Wake goes on to note that if the potential formation of impurities is not evaluated prior to the release of the product, then methods will not be in place to monitor levels. This could lead to a rise or change in profile, which might not be detected until an “effect” in patient population is observed.

“More so, without understanding the stability both of drug substance and drug product, the shelf life cannot be effectively established. This may not only risk the safety and efficacy of a product supplied to patients but can lead to unrealistic or even untenable pricing, especially for biologic molecules, which are expensive to produce, thus impeding their availability,” she adds.

**DESIGNING STABILITY TESTS**

There are several important factors to consider when designing and conducting stability studies.

“Safety, quality, and product efficacy work together in stability studies of APIs and finished drug products. Through stability testing, pharmaceutical companies have the ability to identify and trend shelf life and their effects on efficacy as samples are exposed to time, light, and temperature,” Adam Keisker, supervisor, Laboratory Support Services, Alcami, states.

Degradation factors that are fundamental to consider include physical, chemical, and microbiological factors. Physical factors encompass changes to the physical nature of the drug, such as appearance, properties, hardness, brittleness, and particle size, that occur in tablets, capsules, and semisolids.

From a chemical perspective, scientists look for separation of the chemical compound into elements or simpler compounds or a change in the drug’s chemical nature via hydrolysis, oxidation, isomerization, polymerization, or photodegradation, according to Keisker.

Finally, microbiological contamination of a product, depending on the type of microbe and its level of toxicity, can also play a role in the design and functions of the studies, he adds.

**Degradation factors that are fundamental to consider include physical, chemical, and microbiological factors.**

The strategy used for testing product stability is the most important consideration in the design of a pertinent study, according to Wake.

“If, prior to a formal stability evaluation, work is not performed to understand all potential degradation routes of the molecule through stressed studies, methodologies cannot be effectively chosen for inclusion in the formal study to encompass assessment of degradation product formation and thus all such species monitored,” says Wake.

“For any drug substance or product, an effective stability study cannot be designed on a ‘tick box’ approach for analytical assessments to be included for testing at timepoints,” she adds.

Wake adds that all stability programs should include methods to confirm identity, assay, purity, and impurities. “However, the choice of the actual analysis and number/mode of methods utilized cannot be a ‘standard set’, but should be designed on a bespoke basis.”

“Choice of storage condition or conditions should also be carefully determined prior to initiation. [International Council for Harmonization (ICH)] Q1 and Q5C (1,2) provide guidance on study design for pharmaceutical and biopharmaceutical products and should be the basis for all design; however, the eventual program requires considered input,” explains Wake.

As an example, Wake points out that, if the intended storage condition is refrigerated, this condition should be considered as the long-term storage condition to be evaluated for a minimum of 12 months, typically longer. An accelerated condition would then, in most instances, relate to storage at 25 °C/60% relative humidity (RH) for six months and, importantly, the need for assessment at 40 °C/75% RH, would not typically be required.

“Logistically, the amount of material, drug substance, and/or drug product required to support what can be as long as a five-year program with multiple time points needs to be considered at onset. Not only should this include a realistic amount for the defined program, but should incorporate a minimum of an additional 25% to act as back-up material in case of re-test,” Wake says.

“In addition, ICH guidance requires that a minimum of three batches of material be included in formal stability studies, again
this can put pressure on sample requirement and timely availability,” she adds.

**STRATEGY IN STABILITY TESTING**

Having a strategic approach and considering a plan for a “worse-case” scenario is important to addressing the challenges of stability testing and to conducting a successful testing program. It is also important to approach each study with a bespoke, considered design for storage and testing, rather than a “tick box” approach, Wake says.

“Perhaps the biggest challenge is to ensure that the testing program incorporates sufficient analytics to ensure all potential and known degradants are continually monitored. When considering complex molecules, such as biologics, the complexity of degradation and the number of potential routes makes this assignment extremely difficult,” Wake explains.

If a potential impurity is missed and later seen to appear, this may detrimentally affect the integrity of the stability study. In a worst-case scenario, the missed impurity may require re-testing, which would introduce significant delay to product registration, Wake notes.

“Knowing all the ways a finished product or API could be affected by degradation is crucial in performing successful stability tests. For instance, stability studies are executed to simulate climatic effects. The studies are based on where the products are going to be sold. From those studies, scientists are able to better establish a shelf life of the medicine, determine the best way to store the medicine, and ultimately help ensure the safety of the consumer,” says Keisker.

Analytical methods for effective stability testing vary from drug product to drug product. The design of stability studies must take into account the product form, container type, and packaging, Keisker notes. “For example, commercial drug product testing would include studying the degradation effects from the conditions on both the drug product and the container it is sold in,” he says.

“There are many variables but it ultimately depends on the client and their interests as well as requirements for the climate zone they intend to sell their product,” Keisker adds.

**The nature of stability testing for biologics differs, driven by the complexity of the biologic molecule structure.**

In terms of methodology, most small-molecule pharmaceutical stability study programs are typically based around the need for some analysis that is dependent on the presentation of the substance or product, such as, for example, water content only being necessary on lyophilized or solid material, Wake says. Not all analytics will be required at each timepoint, their inclusion would be driven by the likelihood of change, for example, sterility is typically assessed at six-month intervals, unless a specific indication warrants more frequent analysis.

Typical methodologies for certain quality attributes are illustrated in Table I.

In comparison, for biologics, the nature of the stability testing to be included in any program differs, driven by the complexity of biologic molecule structure. In many ways, biologics require a more diverse analytical capability, according to Wake. Defining a typical stability testing protocol is consequently more difficult, but as a minimum would include assessment of the quality attributes shown in Table II.

“Other criteria such as process related impurities, solvents, metals, etc. are typically not included in a stability program but determined on product release. Again there can be exceptions where there is a potential for the amount of such species to increase on storage,” says Wake.

**IN-USE STABILITY TESTING**

In the case of multi-dose product types, in-use stability testing can be used. The intent of an in-use stability study is to simulate the use of the product in practice, taking into consideration the filling volume of the container, any dilution/reconstitution before use, the hold-time before use, and various diluents that could be used for administration, Crothers says.

The purpose of conducting in-use stability testing is to establish a period of time during which a multi-dose product may be used while retaining quality within an acceptable specification, once the packaging is open or broached, Wake says, citing the European Medicines Agency’s definition of the term (3).

“In-use stability testing can therefore be considered for multi-dose product types, as assessment of the continued efficacy and safety (as defined through critical quality attribute testing) of a pharmaceutical (or biopharmaceutical) drug product...
Once in its final administration form,” Wake says. Typically, an in-use assessment is performed on a minimum of two batches of material, with, ideally, one batch taken from a near end-of-shelf-life product. The protocol involves reconstituting the drug product to its administrative form and testing over a pre-defined storage period at the condition recommended.

“The analytics performed will be in line with those identified for long-term and accelerated storage studies with perhaps a greater influence on microbial criteria and potential impurities derived from pertinent environmental factors, for example, impurities formed through oxygen exposure which is unavoidable in a multi-dose format,” according to Wake.

Establishing an effective in-use shelf-life is of significant benefit. Without such, a multi-dose product design becomes significantly less practical in terms of ensuring patient safety and product efficacy in this format. “This can lead to huge product wastage which, specifically in the case of biological materials, has huge consequence in terms of product cost and maintaining supply which can lead to the product being non-viable in terms of patient access,” says Wake.

Table I. Quality attributes and typical methodology for small-molecule pharmaceuticals.

<table>
<thead>
<tr>
<th>Quality attribute</th>
<th>Typical methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Visual, pharmacopeia method</td>
</tr>
<tr>
<td>Sub-visible particles</td>
<td>As advised in ICH Q4B Annex 3 (R1)</td>
</tr>
<tr>
<td>pH</td>
<td>Potentiometry, pharmacopeia method</td>
</tr>
<tr>
<td>Identity</td>
<td>Mass spectrometry, spectroscopy (NMR/FTIR) or chromatographic retention time.</td>
</tr>
<tr>
<td>Assay</td>
<td>HPLC or GC with suitable detection</td>
</tr>
<tr>
<td>Purity</td>
<td>HPLC or GC with suitable detection</td>
</tr>
<tr>
<td>Impurities</td>
<td>HPLC/GC/IC/ICP—impurity dependent</td>
</tr>
<tr>
<td>Sterility</td>
<td>Microbiology or container closure integrity, Pharmacopeia method.</td>
</tr>
<tr>
<td>Endotoxin and total viable count</td>
<td>Microbiology—Pharmacopeia method</td>
</tr>
</tbody>
</table>

ICH is International Council for Harmonization.
NMR/FTIR is nuclear magnetic resonance/Fourier-transform infrared spectroscopy.
HPLC is high-performance liquid chromatography.
GC is gas chromatography.
IC is ion chromatography.
ICP is inductively coupled plasma.
Source: Intertek

Table II. Quality attributes and typical methodologies for biologics.

<table>
<thead>
<tr>
<th>Quality attribute</th>
<th>Typical methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Visual, pharmacopeia method</td>
</tr>
<tr>
<td>Sub-visible particles</td>
<td>As advised in ICH Q4B Annex 3 (R1)</td>
</tr>
<tr>
<td>pH</td>
<td>Potentiometry</td>
</tr>
<tr>
<td>Identity</td>
<td>Mass spectrometry, immunochromatography or chromatographic/electrophoretic retention/migration time.</td>
</tr>
<tr>
<td>Assay</td>
<td>HPLC or GC with suitable detection</td>
</tr>
<tr>
<td>General Impurities</td>
<td>Reverse Phase HPLC SDS-PAGE</td>
</tr>
<tr>
<td>Impurities (Aggregates)</td>
<td>Size exclusion chromatography (SEC), Analytical ultracentrifugation (AUC), Electrophoresis and/or dynamic light scattering (DLS)</td>
</tr>
<tr>
<td>Impurities (Charge Variants)</td>
<td>Electrophoresis and/or ion exchange chromatography</td>
</tr>
<tr>
<td>Receptor Binding</td>
<td>SPR</td>
</tr>
<tr>
<td>Higher Order Structure</td>
<td>Circular dichroism (CD) and/or spectroscopy (NMR or FTIR).</td>
</tr>
<tr>
<td>Potency</td>
<td>Cell based assay, based on mode of action.</td>
</tr>
<tr>
<td>Sterility</td>
<td>Microbiology or container closure integrity, Compendial approach.</td>
</tr>
<tr>
<td>Endotoxin and total viable count</td>
<td>Microbiology—compendial approach</td>
</tr>
</tbody>
</table>

ICH is International Council for Harmonization.
HPLC is high-performance liquid chromatography.
GC is gas chromatography.
HPLC is high-performance liquid chromatography.
SDS-PAGE is sodium dodecyl sulfate polyacrylamide gel electrophoresis.
NMR/FTIR is nuclear magnetic resonance/Fourier-transform infrared spectroscopy.
Source: Intertek

REFERENCES

Source: Intertek
Process Monitoring and Control Technologies Optimize Operations

Amber Lowry

Over the past several months, manufacturers have introduced and updated products to improve process monitoring and control technologies. Some of these technologies include advances in enterprise resource planning (ERP) software for batch process manufacturing and data loggers for remote monitoring, as well as analytical software, integrated network infrastructure, and control room network solutions. The following is a sampling of such products.

ERP SOFTWARE FOR BATCH PROCESS MANUFACTURING

ProcessPro Global is an enterprise resource planning software solution for batch process manufacturing (1). The system offers full manufacturing, inventory, and financial integration and uses Microsoft service-oriented architecture technologies, including NET and SQL Server. Standard manufacturing, inventory, quality, financial, and sales functions are supplemented with the following features: warehouse management, compliance point of sale, direct store delivery, maintenance and repair, field service, fixed assets, project accounting, payroll, human resources, electronic data interchange, and others.

The solution is available for use in a range of languages, currencies, companies, and industries. According to the company, the software's functional capabilities can be used across multiple industries and countries.
These solutions incorporate technologies from Cisco, Panduit, and Microsoft.

Under the service contract, the company will size, assemble, and test the infrastructure, including configuration and on-site deployment at the serviced facility. Contracts include 24/7 remote monitoring of critical system parameters to help prevent outages and failures, as well as proactive system maintenance and inspections.

The INDS is a network distribution, and is suited to deliver connectivity to a virtualized environment. The IDC provides the hardware and software needed to transition from the company’s original TotalPlant Solution (TPS) control system, enables deployment of the Industrial Internet of Things. Existing control strategies, field terminations, applications, history, and graphics can be retained after installing the upgraded system, according to the company.

Using the company’s Experion Fault Tolerant Ethernet (FTE) infrastructure, the LCN bridge connects Experion to Classic Coax LCN. Once this connection is established, the LCN coax connection can be removed one node at a time. Instead of a hardware connection for each Experion TPS node, only one Experion LCN bridge pair is needed to enable virtualization.

Additionally, the control system can have a common human machine interface and unified physical control network, enabling control devices to integrate with the latest generation of the brand’s automated controllers and safety systems.

The Experion Local Control Network (LCN) solution from Honeywell Process Solutions provides a streamlined control system infrastructure with standards-based functionality, regulatory support capabilities, and integrated plant operations (4). The solution, which is an upgrade from the company’s original TotalPlant Solution (TPS) control system, enables deployment of the Industrial Internet of Things. Existing control strategies, field terminations, applications, history, and graphics can be retained after installing the upgraded system, according to the company.

Using the company’s Experion Fault Tolerant Ethernet (FTE) infrastructure, the LCN bridge connects Experion to Classic Coax LCN. Once this connection is established, the LCN coax connection can be removed one node at a time. Instead of a hardware connection for each Experion TPS node, only one Experion LCN bridge pair is needed to enable virtualization.

Additionally, the control system can have a common human machine interface and unified physical control network, enabling control devices to integrate with the latest generation of the brand’s automated controllers and safety systems.

DATA LOGGERS FOR REMOTE MONITORING

Digi-Sense data loggers from Cole-Parmer are suited for the remote monitoring of critical environments (5). The products are equipped with the company’s subscription-based TraceableLIVE wireless technology, which connects to data via WiFi on a smartphone, tablet, or personal computer. The cloud-based interface allows workers to view conditions in real-time; set alarm parameters; view data logging history; generate data reports in real time; receive email, text, and push notifications; and receive alerts for temperature alarm, connectivity interruption, and low battery warning.

The devices come in four models that include NIST [National Institute of Standards and Technologies]-traceable calibration for measurement reliability. The Temperature/Humidity model has a range of 32-131 °F (0-55 °C) while the Ultra-Low Temperature model measures down to –130 °F (–90 °C). The Multiparameter model measures temperature, humidity, carbon dioxide, or barometric pressure levels, and the Refrigerator/Freezer Thermometers include a choice of four different temperature probe styles.

REFERENCES

Bio/Pharma Serialization Nears a Tipping Point

Agnes Shanley

For more than a decade, the bio/pharmaceutical industry has struggled to establish a true electronic pedigree that would allow its products to be traced and verified at any point along the supply chain. The US Drug Supply Chain Security Act (DSCSA) and the European Union’s Falsified Medicines Directive set timelines and requirements for serializing product packaging, aggregating product and lot-level transaction data electronically, and sharing information with distributors and at the point of use or sale.

Even though serialization is only the first leg of the journey toward full traceability, the technical challenges and costs are significant. This is due to a “fundamental mismatch of applied integration technologies for inter-plant, plant-to-enterprise, and distribution repack exchanges,” says Charlie Gifford, technical director of the Open Serialization Communication Standard (OPEN-SCS) Working Group.

INTERRELATIONSHIPS BETWEEN DATA
In addition, he says, distinct data elements required for serialization and traceability are interrelated. Examples include workflow rules; serial number formats; data sets (i.e., those established by regulators vs. those used by vendors vs. those for users); provisioning and serialization events; master data...
and associated technologies (e.g., for production, ordering, and reporting) so the data and their relationships must be agreed upon and specified for data accuracy and exchange interoperability. Understanding and agreeing on data relationships across the overall serialization process is extremely challenging, Gifford says.

**OPEN STANDARDS**
Four large life-sciences companies and five solution providers established the OPEN-SCS working group in February 2015 to sort through these issues. Their goal was to stem pharmaceutical counterfeits by developing open, vendor-neutral data-exchange solutions that would simplify integration of the components and systems required for product serialization and traceability.

The group now has more than 25 active members and 100 interested supporters. OPEN-SCS achieved a number of important goals in 2017 (see Sidebar), establishing a collaborative agreement with the International Society for Pharmaceutical Engineering (ISPE) and approving the first version of the OPEN-SCS Packaging Serialization Specification (PSS 1.0).

**Plans call for OPEN-SCS to release Good Automated Manufacturing Practices (GAMP)-compliant user requirement specifications (URS), functional specifications (FS), and operational and installation qualification (OQ/IQ) templates in March 2018.** A core group of vendors (ACG Inspection Systems, Avanço, Antares Vision, Arvato Systems, Optel Vision, Systech, TraceLink, Tradetivity, Uhlmann, Vantage Consulting, and Wipotec-OCS) are developing validation test interfaces for one or more of the four use cases of PSS 1.0, says Gifford. Each vendor may commercialize compliant interfaces by the end of the third quarter of 2018, he says.

A readiness gap still separates large pharma companies that are ready for serialization from small generics and CMOs that aren’t.

### REDUCING COSTS IS CRUCIAL
The group expects these efforts to reduce the cost and time

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**Surveys redefine “ready”**

In December 2017, TraceLink released findings from a survey of 660 serialization partners, including 174 pharmaceutical companies and 155 contract manufacturing organizations (CMOs) (1). Results, due to be published during the first quarter of 2018, suggest that only one third of the pharma company and CMO executives surveyed see their companies as being “very ready” for the US Drug Supply Chain Security Act (DSCSA) serialization deadline in November 2018.

Most of the companies who feel well prepared had taken many of the necessary steps, but there were some notable gaps. For example, only 8% had integrated efforts with most (i.e., 81–100%) of their CMOs. Only 11% reported that 81–100% of their CMOs were ready to ship serialized product, while only 12% reported that internal packaging line equipment had been ordered and fully installed, and that 81–100% of their internal packaging lines were ready. In addition, 23% were not concerned about equipment and skills shortages affecting serialization compliance, and only 37% had moved away from paper-based lot transaction records. Half of CMOs surveyed felt very ready for DSCSA, but only 23% reported that they are integrated with their pharma customers, while 22% say brand owners are ready for integration. Only 9% are concerned about equipment shortages having an impact on compliance. For pharma companies and CMOs, only one third reported feeling “very ready” for the EU’s Falsified Medicines Directive (FMD).

An earlier 2017 survey (2) by the Healthcare Distributors Association examined the industry’s readiness for serialization based on responses from professionals at 67 manufacturers, including 15 of the top 20 based on product sales. This survey also found readiness gaps, with 3% of generics and 34% of branded-product manufacturers expecting to ship 100% serialized product to distributors by November 2017. By November 2018, however, 69% of generics and 91% of branded pharma companies are expected to do so.

By November 2017, 24% expected to send serialized data to distributors, 33% said they will send it by November 2018, and 30% expect to send it between 2018 and 2023. However, 13% are unsure that they will send serialized data.

**References**
It was a busy year for the Open-SCS working group. Charlie Gifford, technical director of the group, summarized developments that occurred in 2017.

**BioPharm International**: How did you decide to use good automated manufacturing principles (GAMP) lifecycle best practices for the serialization standards?

**Gifford**: The User Requirement Specification (URS) and Functional Specification (FS) for the standard Packaging Serialization Specification (PSS) version 1.0 were approved by members in August. Three member companies are already using them as templates for projects, and providing feedback into ongoing validation testing.

However, in June, we took the International Society for Pharmaceutical Engineering’s (ISPEs) recommendation and adopted the GAMP lifecycle best practice of conducting a full validation test and report using prototype OPC-UA interfaces in order to refine PSS 1.0’s URS, FS, and operational and installation qualification (OQ/IQ) templates. The new PSS 1.0 package is set for formal release in March 2018, depending on available member resources. Eleven vendor members have committed a developer to build prototype interfaces for the validation test. This design-build-test exercise has already brought out many updates to functional requirements that had not been addressed in the previously approved draft.

In December, work began on a PSS 2.0 URS working draft, which is scheduled for member review in February. Six inter-plant solution providers and two end users are working on this project. Depending on availability of member expert resources in 2018, the technical committee hopes to accelerate and release PSS 2.0 by the fourth quarter of 2018.

**BioPharm**: What kind of participation are you seeing among pharma companies and contract manufacturing organizations (CMOs)?

**Gifford**: Membership is now over 25, with 100 interested companies saying that they will join the group, either when PSS 1.0 is released addressing plant operations (Level 3), to enterprise (Level 4) exchange use cases for regulation reporting, or once the PSS 2.0 addresses Level 2-Level 3 exchange use cases.

**BioPharm**: What have been the most challenging technical aspects of developing this standard? How are they being resolved?

**Gifford**: One major challenge was dealing with the high-level complexity of the packaging serialization scope and problem data (product, order, reporting) and their associated integration technologies. As we’ve learned after working on these problems for the past 24 months, the root of the problem often lies with pharma customer requirements. Most pharmaceutical manufacturers’ serialization exchange requirements force their vendors to customize GS1’s Electronic Product Code Information Services (EPCIS) schema into forms that are not interoperable across systems. These interfaces don’t scale, corrupt good data, and do not apply required interoperable transaction methods. GS1’s EPCIS experts have worked directly with our team to ensure that the PPS 1.0 [specifications for each use case] comply with EPCIS, or at least are as closely aligned as the scope permits.

Because EPCIS’s scope does not address serial number management and serialization events between the packaging plant and enterprise, another major challenge was developing a Serialized Identifier (SID) event lifecycle model for the events, states, and transition for serial number management and serialization events between the packaging plant and enterprise. Along the way, we’ve had to respond to the challenge that any new collaborative organization faces: how to fund all this work. We are still working to find the best business model that will support new projects and updates from changed and new regulations.

**BioPharm**: How difficult has it been to establish consensus among members from such different groups?

**Gifford**: It was especially challenging during 2015 and 2016, when there was a great deal of debate on whether PSS 1.0 should address data exchange between the site serialization manager-actor (Level 3) and the enterprise serialization manager-actor (Level 4) or between the packaging line serialization manager-actor (Level 2) and Level 3. We held four workshops on this topic alone during that period.

**BioPharm**: How difficult is it to get the high-level IT help that serialization and traceability programs demand?

**Gifford**: Hiring skilled developers, for the funding that is available, is a challenge for all manufacturing and business sectors, especially as Manufacturing 4.0 initiatives take shape. Integration-specific developers are a rare breed. They need to have over five years of experience and mentoring in order to be competent enough not to compromise data accuracy and security. This challenge has dramatically affected the quality of serialization solutions deployed in the life-sciences industry. Having a standardized integration approach will significantly reduce risks.

At this point, though, life-sciences companies are not openly acknowledging and reacting to the supply of talent. For example, the going hourly pay rate for developers with the necessary skills has increased to $180-200 per hour. Pharma companies are paying $80-120 per hour, so many developers in life sciences get serialization experience and additional training and leave the sector for better-paying jobs elsewhere.

**BioPharm**: What have you learned from the pilot tests?

**Gifford**: We achieved a number of benefits by using OPC Universal Architecture (UA), which allowed us to find and fix holes in the original draft standard specifications. We used UA to develop the validation test, FS, and associated OQ and IQ modules. The validation tests have provided a foundation for certification programs, and, as previously mentioned, solutions providers are participating in the validation test by developing interfaces.

**BioPharm**: What are you planning for the next phase of this work?

**Gifford**: We began working on a draft of the PSS 2.0 URS in December for review by members in February or March. The approved scope of this standard specification will extend use cases for serial number provisioning and return as well as serialization master data, and event reporting. It will also address use cases for rework and multistep processing and incorporate new use cases determined through customer surveys and an April 2017 workshop, including serial number provisioning for lot start; end-of-lot issues such as unused serial number returns and unused, decommissioned, orphaned, or sampled serial numbers; end-of-lot issues with full batch data and mid-lot runs; production order downloads for new and rework orders, including aggregation hierarchies; and handling exceptions.
required to implement serialization and traceability projects by at least 50% when applied across multiple packaging plants. “For most companies today, integration typically means custom projects,” says Evren Ozkaya, founder and CEO of Supply Chain Wizard. “OPEN-SCS will improve the standardization of exchanged data and their data structure in communications between plants, and between plant and enterprise systems, which will reduce cost.”

Reducing integration complexity and cost will be crucial to advancing traceability initiatives within smaller pharmaceutical companies, especially generic-drug manufacturers and smaller contract manufacturing organizations (CMOs), whose margins are extremely tight.

“These companies don’t typically see any direct benefits by investing in expensive systems to track their products throughout the supply chain,” says Marcel de Grutter, OPEN-SCS executive director. “Even major multinationals struggle with the fact that they are currently releasing fewer blockbusters so they are continuously restructuring to support their commercial products,” he says. As a result, implementations are delayed, as serialization competes with priorities such as ensuring a continuous supply of product. In 2017, after realizing that many smaller firms had not even begun serialization efforts, FDA extended DSCSA’s original serialization enforcement deadline by one year, to November 2018 (1).

**BRIDGING THE READINESS GAP**

Still, a readiness gap remains underestimated. Most large pharma companies are ready, or were a while ago, but some companies still haven’t begun formal serialization programs, while others that see themselves as ready have only serialized part of their packaging lines, says Ozkaya (see Sidebar). “Painful days are ahead of them,” he says, because serialization efforts can lower productivity and line efficiency during early implementation stages.

The number one issue is CMO readiness, says Ozkaya. “FDA’s enforcement delay was a welcome move, but companies need to staff project teams properly, partner more closely with solution providers, and manage their internal site and external CMO compliance risks more proactively,” he says.

Observers see industry mind-
Single-Use Filling Assemblies for Aseptic Fill/Finish Applications

AdvantaPure’s sterile-molded filling assemblies are suited for single-use vial and syringe filling. The products are made from AdvantaSil silicone tubing and molded components, or weldable and sealable AdvantaFlex biopharmaceutical tubing and components. The assemblies are completed with bags, filters, sterile connectors, filling needles, and other accessories. The assemblies also are supplied sterilized and ready to use, and feature smooth, molded junctions for continuous flow and to reduce leak and entrapment issues associated with barbed fittings. The multiport tri-clamp design helps reduce potential leak points and minimizes holdup volume, according to the company.

AdvantaPure
www.advantapure.com

Additional Size for Quaternary Diaphragm Pumps

PSG, a Dover company, has expanded its Quattroflow line of quaternary, four-piston diaphragm pumps to include the QF10k size pump. The pump has been designed to fill the gap between the existing QF4400/5050 and QF20k pump sizes and provides a maximum flow rate of 10,000 lph. Product features include a stainless-steel pump chamber design, a maximum pressure of 6 bar (87 psi), 20:1 turn-down ratio, linear flow performance, and high-flow stability even at low flow rates. Additionally, the pump offers clean-in-place/steaming-in-place and autoclave capabilities. Available accessories include control box, power box, diaphragm sensor, and proportional–integral–derivative controller. Typical applications include chromatography and cross-flow filter systems.

Wilden
www.psgdover.com/en/wilden

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WXII Biologics, info@wxibiologics.com, www.wxibiologics.com

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Q: Given the current focus on the subject of data integrity in regulatory inspections, we have performed an internal assessment. We found several pieces of equipment, in particular analytical instruments, which do not meet the requirements (e.g., shared user access). We are concerned whether we can continue using this equipment under these circumstances. Can you advise?

A: Although data integrity is not a new concept, it is true that there has been an increased focus on data integrity in inspections by regulatory agencies globally, and this is very likely to continue unabated. You certainly did the right thing by assessing your current compliance level, which, it turns out, is not in substantial compliance with the regulations.

First, you must determine whether it is acceptable to continue to use these non-compliant systems for the manufacture of pharmaceutical products, and if so, under which circumstances. The regulators encourage a risk-based approach to compliance, though this must not be misinterpreted as being allowed to be non-compliant, rather, this compliance approach requires you to perform a risk assessment (i.e., you need to ascertain the risk to the patients should you continue using your out-of-compliance equipment).

Take for example, a tablet press that has been in operation for 15 years, which is in perfect working order and has no access controls. Anyone working on the machine can change the parameters and edit the stored data. This is not an acceptable situation. Preferably, one would implement technical solutions (perhaps a software upgrade), but where this is not an option or would take too long, one needs to consider procedural remedial actions. In this instance, this could include the verification of the settings by a second person, plus an amendment to the operating procedure, which would clearly define acceptable and unacceptable data handling (e.g., changing parameters). If neither technical nor procedural solutions lead to an acceptable risk level, I’m afraid, this piece of equipment must no longer be used.

Another example would be the use of a laboratory information management system (LIMS) by several operators sharing a user ID and password. If this is the case because of cost savings (purchasing a minimum number of licenses only), then this issue can be remedied almost immediately by purchasing the appropriate number of licenses and revising the operating procedure to mandate individual user IDs and passwords for all LIMS operators.

You did the right first step (i.e., assessing the as-is situation); however, you should not stop there. Now you must implement a company-wide data integrity policy and embed data integrity into your quality management system. Only by taking data integrity seriously, and implementing the appropriate processes, procedures, and systems within your company, will you be able to achieve full compliance with the data integrity requirements. This will give you peace of mind when an agency inspector calls next time. ☞
Infection initiated at 6:15 PM.

Harvest triggered at 1:30 AM.

Harvest completed at 3:12 AM.

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