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Internal and External Challenges to Pharma in 2019

Rita Peters

Pricing pressures, investment volatility, and government dysfunction greet Pharma in 2019.

Good news about a record-setting number of new drug approvals in 2018 was tempered by financial and political pressures external to the industry. Questions on Bio/Pharma’s 2019 agenda include pressure to lower drug prices and contain costs, and deal with a volatile investment market and contentious federal government.

In an annual GlobalData outlook report (1), 51% of respondents said drug pricing and reimbursement constraints will have the greatest negative impact on the pharmaceutical industry in 2019. While some drug companies self-imposed price freezes in 2018—under pressure from the Trump Administration and Congress—many kicked off 2019 with price increases for more than 100 drugs averaging 6.3%.

Investment options
The investor market resembled a roller coaster in 2018, ending on a downward trend. The Vantage 2019 Preview report (2) said it was difficult to predict how much further the market may fall, and those interviewed for the report expected a more volatile year.

Companies looking for funding will have to work harder in 2019, but the report says financing options are not expected to dry up. While there is enthusiasm over new therapies, these products must prove commercial success to maintain investor interest in biologic products, the report said.

A Deloitte report (3) in mid-2018 said the majority of US companies were interested in investing in R&D, business operations, and capital projects, including some US operations, as a result of the corporate tax reforms of the Tax Cuts and Jobs Act enacted in December 2017. The bio/pharma executives surveyed said they were likely or very likely to invest in R&D (67%), capital projects (57%), general business operations (50%), share buybacks (50%), and M&A (42%). Lower priority investments were compensation/pension funding (40%) and hiring (40%).

Big deals
The 2016 presidential election and tax reform debate of 2017 put some mergers and acquisition activity on hold, according to the Deloitte report; however, deals picked up in the first half of 2018.

In three weeks spanning the end of 2018 and start of 2019, several large deals were reported. Pfizer and GlaxoSmithKline announced on Dec. 19, 2018 that the companies will merge their consumer healthcare products businesses and form a separate consumer-focused company. On Jan. 7, 2019, Eli Lilly announced an agreement to acquire Loxo Oncology for $8 billion. And, in one of the largest pharma acquisitions ever, Bristol-Myers Squibb announced on January 3 that it will acquire Celgene in a cash and stock transaction valued at $74 billion.

Restructuring FDA?
While the pharma industry—and the rest of the nation—awaited a resolution to the partial government shutdown, a white paper (4) based on input from seven former FDA commissioners, recommended FDA be reconfigured as an independent federal agency. A new structure is needed, they argued, to promote science-based decisions, increase transparency, streamline processes for developing regulations and guidance documents, and allow for more responsive and predictable decision making.

The white paper stopped short of recommending a new model for agency operations but defined several major shortcomings of current operations. With federal government operations on hold over political squabbling, it was nice to see constructive efforts to address what ails the industry.

References
4. The Aspen Institute, Seven Former FDA Commissioners Recommend: FDA Should be an Independent Federal Agency, White Paper, January 2018. PT
Save the date for PDA’s inaugural Biopharmaceuticals Week, May 6-10 in Long Beach, CA.

This exciting new week-long meeting format features three events focused on biopharmaceutical manufacturing, including:

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Improved Mixer Lift and Seal Designs

Charles Ross & Son Company has made improvements to the dual-post hydraulic lift and seal design of its 1500-gallon Multi-Shaft Mixer Model PVM-1500. The new lifting design is a double-acting, fully hydraulic cylinder operating at a higher pressure, allowing for a smaller cylinder and less oil for operation. David Hathaway, vice-president of Ross Engineering, states that with the new design, the lifting system provides faster lifting speed when raising and lowering the agitators.

The new seal arrangement allows seal replacement without removing agitator shafts. Unlike the historical design, seal replacement no longer requires removal of the mixer from the tank or tank entry to access the seal.

The PVM-1500 features three independently driven agitators: a screw auger, a high-speed disperser, and a three-wing anchor agitator. The sides and bottom of the changeable mixing vessel are insulated and jacketed for up to 50 psig. According to the company, this vacuum-rated machine can run continuously and is supplied with rugged touchscreen controls showing digital readouts for speed, cycle time, vacuum level, and batch temperature.

Ross, Charles & Son
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Tabletop Spray Dryer

Fluid Air’s portable PolarDry Electrostatic Spray Dryer Model 0.1 is compact in size while retaining the same features of previous spray dryers. The spray dryer’s smaller dimensions allow the system to fit inside spaces such as most lab fume or containment hoods.

The dryer produces small-scale samples with minimum product loss and can be easily disassembled for autoclave sterilization, the company reports. The system is compatible with optional high temperature and ultrasonic spray drying nozzles that ensure efficient microencapsulation. The ultrasonic nozzle is suited for creating small particles less than 10 microns, and formulators still have the choice to use the Model 0.1 as a standard spray dryer with two fluid nozzles. Other features include a programmable logic controller system with data-logging, zero need for an atomizing heat, and low volatility loss.

Fluid Air
www.fluidairinc.com

Microplate Spectrophotometer

The Epoch 2 Microplate Spectrophotometer from BioTek Instruments has added features that include monochromator-based individual wavelength selection or wavelength scanning from 200–999 nm to accommodate a range of assays, including nucleic acid and protein quantification, enzyme-linked immunosorbent assay, microbial growth, endotoxin, reactive oxygen species assays, and enzyme kinetics. New onboard software eliminates the need for a separate computer and includes predefined common protocols for rapid assay setup and recall. Custom protocol definition, storage, and selection are easily accomplished via the optional color touchscreen interface. Endpoint, kinetic, and spectral scanning applications are all available from the touchscreen; data can be output to a USB flash drive or printer.

The spectrophotometer is compatible with 6- to 384-well microplates and cuvettes as well as the company’s Take3 Micro-Volume Plate for dilution-free nucleic acid quantification in volumes as low as 2 μL. Advanced shaking profiles include linear, orbital, and double orbital, and 4-Zone incubation to 65 ºC and Condensation Control facilitate temperature-sensitive assays.

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CDER Priorities for 2019: Opioids, Quality, Safety, and Innovation

Jill Wechsler

FDA plans to support initiatives to ensure that all medicines are safe, effective, and of high quality.

Ensuring quality

CDER has launched a two-year program to improve oversight of drug safety, featuring new methods to evaluate the more than two million adverse event reports received in 2018 on marketed drugs. The agency is pressing drug companies to comply more fully with GMPs through more targeted inspections and recalls for those failing to meet standards. Drug compounding pharmacies and outsourcing facilities will remain in the spotlight in 2019, as FDA inspectors continue to find violations at these operations. A related initiative is to continue to implement requirements for tracking drugs through the supply chain to detect unauthorized medicines, an effort designed to have “a big impact on the gray market,” Woodcock commented. CDER’s Office of Pharmaceutical Quality (OPQ) will continue to seek more timely inspections of manufacturing facilities, a process that should be facilitated by a new inspection protocol for drugs, beginning with sterile drug manufacturing facilities.

These efforts may be enhanced by visible progress in industry implementing advanced manufacturing systems. Woodcock noted at the Summit that five firms have filed applications with continuous manufacturing components, and that generic-drug makers are moving in this direction. Other federal agencies support such efforts as a way to enhance surge capacity when additional treatments are needed to manage infectious disease outbreaks or bioterrorism attacks. OPQ also aims to launch a structured approach to the manufacturing supplement review process to better manage product changes through the drug lifecycle.

Accelerating approvals

An important goal for Woodcock is to complete the overhaul of the new drug review process. She recently named Peter Stein director of the Office of New Drugs (OND), and long-time CDER guru Bob Temple will become OND senior advisor, positioned to address the more controversial and difficult drug development and review issues. Woodcock hopes to finalize the OND reorganization by next summer, but it has been delayed by difficulties in gaining Congressional approval of a new user fee program for improving the regulation of over-the-counter drugs.

Modernizing the review process will involve implementing new automation tools for managing drug applications, study data, and review documents under a “multi-disciplinary, issue-based review document” system. CDER also will continue to carry out provisions of the 21st Century Cures Act and reauthorized user fee programs to further advance patient-focused drug development, expanded use of real-world evidence, novel clinical trial design, and added authorities to hire more experts needed to carry out these multiple drug regulatory programs.

Reference


Jill Wechsler is Pharmaceutical Technology’s Washington editor, jillwechsler7@gmail.com.
Digital health became an increasingly important focus area for FDA in 2018. After launching the Digital Health Innovation Action Plan in 2017, which is seeking to modify the agency’s approach to digital health products (1), FDA formed the internal data science incubator, the Information Exchange and Data Transformation (INFORMED), in 2018. The agency has also proposed to create a Center of Excellence for Digital Health in its Fiscal Year 2019 Budget.

Also in 2018, FDA approved the first medical device that combined a special camera and artificial intelligence to detect greater than a mild level diabetic retinopathy in adults who have diabetes in a primary care setting (2) and permitted the marketing of an artificial intelligence algorithm for aiding providers in detecting wrist fractures (3). Most recently, FDA awarded de novo clearance to Apple’s Series 4 model of the Apple Watch (4).

FDA Commissioner Scott Gottlieb has indicated that digital technology requires “a reimagination of healthcare delivery” (1). The agency is committed to fostering, not hindering, innovation in digital health technology. Gottlieb hopes the new Center of Excellence will “help establish more efficient regulatory paradigms, consider building new capacity to evaluate and recognize third-party certifiers, and support a cybersecurity unit to complement the advances in software-based devices.”

From artificial intelligence technologies such as deep learning and natural language processing to smart devices and advanced software and apps, digital technologies will clearly play an increasing role in drug and medical device development going forward.

References

—Cynthia A. Challener, contributing editor

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A 2003 *Wall Street Journal* article noted a pharmaceutical industry “secret,” as the industry develops “futuristic new drugs, its manufacturing techniques lag far behind those of potato-chip and laundry-soap makers” (1). Since the article was published, the introduction of quality-by-design practices, new monitoring technologies, and advances in science and engineering have improved some bio/pharma manufacturing processes. In too many cases, however, manufacturing and quality practices are still inadequate or too expensive.

The number of drugs approval by FDA—as well as innovative “firsts” designed to address patient needs—accelerated in the past two years. Following the 2017 approvals of the first cell therapies and gene therapies, 2018 saw the approval of new treatments for infections, the first novel antiviral treatment for the flu in 20 years, the first drug with an indication for treatment of smallpox, the first non-opioid treatment for the management of opioid withdrawal symptoms, and the first drug that contains a purified drug substance derived from marijuana.

The upswing in approvals of novel therapies indicates that bio/pharma companies are embracing innovation in R&D. However, analysts report that R&D efforts show diminishing returns. And, the ongoing pace of FDA warning letters, observations, recalls, and drug shortages demonstrates that the bio/pharma industry still has work to do to achieve efficient, cost-effective manufacturing, quality, and analysis to ensure a safe, sufficient drug supply.

A Deloitte/GlobalData study (2) reported that R&D returns at 12 Big Pharma companies hit 1.9% in 2018, the lowest level in nine years, down from 10.1% in 2010. Costs to bring a biopharmaceutical drug to market have almost doubled since 2010 from $1.18 billion to $2.18 billion while forecast peak sales per asset have fallen from $816 million in 2010 to $407 million in 2018, the report notes.

Four small, specialized biopharma companies analyzed for the report fared better than the Big Pharma companies with returns on R&D of 9.3%. Higher development costs ($2.8 billion) were offset by higher anticipated sales ($1.17 billion).

In light of ongoing criticism of the high cost of drugs, raising prices may not be the answer; bio/pharma companies need to find innovative ways to improve efficiencies.

**Warning signs**

In 2016, the number of warning letters issued by FDA for good manufacturing practice infractions doubled and maintained that high level in 2017 and 2018. The number of drug products recalled by FDA’s Center for Drug Evaluation and Research (CDER) has declined in the past two years; however, the number of recall events increased to the second highest level in the past 10 years (3). While efforts over the past five years have cut the number of new shortages from 251 in 2011 to 35 in 2017, as of Jan. 3, 2019, FDA listed 114 drugs as “currently in shortage” and 207 as discontinued (4).

Two examples demonstrate the implications of substandard quality and ineffective drug manufacturing on patients and company bottom lines.

Recalls of angiotensin II receptor blocker (ARB) drug products due to the presence of probable human carcinoens traced to API manufacturers—due to the presence of probable human carcinogens—were launched in 2018 and continued in early 2019. As the recalls widened, regulatory authorities around the world scrambled to identify the root cause of the impurities and implications for patients.

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Bio/Pharma Manufacturing

hospitals, seven health organizations representing 500 US hospitals formed Civica Rx, a not-for-profit generic drug company; the new organization plans to manufacture drugs for use by patients at the member hospitals. In September 2018, the company announced that it has identified 14 hospital-administered generic drugs and will either directly manufacture generic drugs or sub-contract manufacturing to contract manufacturing organizations (5).

The Deloitte study authors stressed the need for a “transformational change” in R&D productivity that uses technology—artificial intelligence, robotic process automation, natural language processing and generation, and machine learning—to replace or augment work done by humans. Partnerships, collaborations, and non-traditional operational models will be necessary to compete in a digital environment and companies will have to compete with non-pharma organizations for the technical talent needed to operate a digitally-driven company.

Many of the predicted applications of information technology focus on drug discovery, clinical trial, and patient monitoring applications. There are, however, opportunities to adopt other new technologies for drug formulation, process development, manufacturing, and supply chain phases.

Advanced manufacturing technology needed

While bio/pharma companies have demonstrated success at turning out new therapies, the uptake of advanced manufacturing technologies to produce these products, or better ways to manufacture existing products, has been slower.

Manufacturing issues, delays or capacity issues, and loss of manufacturing site account for two-thirds of the causes of drug shortages, FDA reports (6). Capital costs, lost production time for retrofitting, and the need for regulatory review for process changes deter some companies from investing in new technologies for established product lines. The urgency to get a new drug to market is incentive to stick to proven technologies that may not be efficient or cost-effective in the long term.

Some advanced manufacturing technologies—such as continuous manufacturing for solid-dose drugs, 3D printing of drug products, and single-use bioreactors—have demonstrated effectiveness. Recent FDA approvals of continuous manufacturing processes for oral solid-dose drugs has spurred interest and innovation for advanced manufacturing processes. The Engineering Research Center for Structured Organic Particulate Systems (C-SOPS) at Rutgers University (NJ) works with industry and FDA to modernize pharmaceutical manufacturing processes focusing on continuous processing with predictive control and the next generation of dosage forms.

“There is a lot of technology out there, but the largest challenge remains in bringing it all together in a timely and cost-effective manner,” says Douglas B. Hausner, associate director of C-SOPS. “This is a challenge with modern advanced methods that have greater complexity and require greater upfront effort and investment to then run smoothly thereafter. Much of this pertains to software, sensor, and control integration. Some companies are looking to form partnerships and ‘pre-integrate’ where possible to minimize this.”

Many technological advances and materials are needed to reduce the costs of biopharmaceutical manufacturing, says Ruben G. Carbonell, chief technology officer at the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL), a public-private partnership that advances biopharmaceutical manufacturing innovation and workforce development. In-line process analytical technology (PAT) for product quality and process control is one of the areas of greatest need, to enable continuous and hybrid processes, he says.

Automated bioreactors and purification processes for cell-therapy manufacturing; rapid adventitious agent (AA) detection and novel materials for viral clearance; and other technologies to reduce release times for biotherapeutics are other areas of need, he says. The availability of advanced technologies does not necessarily mean they are widely adopted, however. For example, “significant advances are being made in rapid AA detection utilizing next-generation screening that are yet not being broadly throughout the industry,” Carbonell explains.

The equipment, instrument, or process-related steps that bio/pharma should take to improve development and manufacturing varies from organization to organization based on a number of factors, Hausner says. “In general, though, for powder-based manufacturing, an investment in physical property characterization coupled with advanced data analytics of the resulting data can greatly improve organizational familiarity with ingredients and what works for various applications. This enables organizations to gain formulation manufacturability experience, which is additive, and can greatly expedite process development over time.”

The fear of being first

Bio/pharma companies operate in a regulated environment and face pressures to control end-product prices while driving investor return on costly R&D efforts. The tendency to take a conservative approach to the adoption of new technologies or materials is not surprising.

“There are significant efforts within large biopharma companies and suppliers in the testing and evaluation of novel approaches to cost-effective manufacturing,” says Carbonell. “Adoption of these technologies has been slow because of perceived risks of not being approved for new products or processes.”

Hausner notes that when assessing new technologies or processes to advance drug production, companies are initially cautious and calculated, skeptical of regulatory acceptance, followed by enthusiasm and looking for rapid solutions and regulatory clarity.

“Given the significant costs associated with biopharmaceutical products, it is not surprising that biopharma companies take a conservative approach to innovation because they strive to ensure

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Erika Riehle
Sr. Clinical Supply Chain Manager, Fisher Clinical Services
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acceptance by regulatory agencies,” says Carbonell. “One of the main barriers to adoption of new technologies is indeed the perceived risk of not achieving regulatory acceptance. The biopharma industry, manufacturers and suppliers, should work side by side with regulatory agencies to evaluate new technologies to ensure rapid adoption.”

“There is the obvious financial cost/benefit and the fact that unknowns and unproven tech are always harder, but beyond this it often seems to come down to organizational readiness,” says Hausner. “Many new technologies are complex and require additional expertise often in the form of new hires or at least vendor/consultant relationships. There needs to be true organizational buy in for an advanced integrated technology. It can be much closer to buying or building a new plant than a new piece of hardware like a tablet press.”

**FDA funding to fuel innovation**

FDA actively encourages the adoption of advanced manufacturing processes. In 2014, the agency initiated an Emerging Technology Program, which enables meetings between drug development companies and FDA Emerging Technology Team members to address potential concerns about a novel technology prior to filing a regulatory submission.

While the agency has issued guidance on emerging technologies and promotes the adoption of advanced technologies at industry meetings, a broader effort by the agency is needed, wrote FDA Commissioner Scott Gottlieb in a July 2018 blog.

“The bottom line is this: drug makers won’t switch to these systems until we create a clear path toward their adoption and provide more regulatory certainty that changing over to a new manufacturing system won’t be an obstacle to either new or generic drug approvals,” wrote Gottlieb. “The FDA recognizes that it’ll require additional investment in policies and programs that’ll provide regulatory clarity to

**Addressing external pressures**

Drug companies have traditionally outsourced research, development, or manufacturing processes to gain needed expertise and expedite development and manufacturing. What role can the contract services market play in improving drug development and manufacturing? What industry trends are impacting manufacturing strategies? Fiona Barry, associate editor, PharmSource, a GlobalData product, shared industry research perspective on strategies to reduce production costs, the impact of reimbursement policies, and global regulator collaboration with *Pharmaceutical Technology*.

**PharmTech**: The call by government officials, payers, and patients to reduce drug prices will pressure drug companies to produce products more cost-effectively. Will pressures to reduce drug prices encourage or discourage innovation? What are some strategies to reduce production costs?

**Barry (PharmSource, a GlobalData product)**: We predict a ‘Starbucks approach’ to speeding new molecules through development while maintaining quality, as biopharma companies, especially those with a large-molecule pipeline, take advantage of technology and outsourcing to make production cheaper and more efficient.

When it comes to making decisions about investments in bioreactors, biopharma companies will ‘scale out’ to contract manufacturing organizations (CMOs) rather than ‘scale up’ internally.

Scale-up can throw up unexpected costs and quality problems. Companies will be able to prevent this by choosing a bioreactor size early in the development process, and then increasing the number of batches; this avoids committing to a larger facility that might turn out to be unnecessary.

Recent developments—like GE HealthCare’s KUBio mAb facilities—show flexible biologic facilities can be built and put into operation in under two years. This approach will allow flexibility around market size, and even means companies could create plants when and where they are needed, instead of using a single facility to support the global market.

**PharmTech**: What do changes in other sectors of the drug development continuum, such as real-world evidence, biomarkers for clinical trials, and new reimbursement schemes mean for the drug formulation, process development, and manufacturing sector?

**Barry**: The industry is starting to consider more carefully the effect reimbursement policies are having on pharma manufacturing. FDA Commissioner Scott Gottlieb announced this summer a task force to look into this question.

Gottlieb cited the problem that reimbursement policies by Medicare and Medicaid and other payers could be making it difficult for companies to manufacture certain drugs profitably.

Another problem is that the current set-up inadvertently discourages drug companies from manufacturing drugs that are more likely to go into shortage, so it is likely the FDA will tackle this problem with financial incentives.

**PharmTech**: What actions can regulatory authorities take to help transform bio/pharma development and manufacturing?

**Barry**: The major national regulatory authorities are generally very open to innovation that helps the industry and keeps patients safe. For instance, the mutual recognition agreement (MRA) program allows the FDA and regulators of select European Union countries to recognize each other’s inspections.

The scheme has now spread to 21 countries following the addition of Belgium, Denmark, Estonia, Finland, and Latvia in November 2018. If regulators spread it to the rest of the EU, this would be a great step for industry and regulators alike: by avoiding duplicate inspections, compliant facilities would be spared from unnecessary visits, and regulators’ resources will be freed up to focus on problem plants.

As manufacturing markets mature in the rest of the world, MRAs could spread even further. Regulators seem open to this: for instance, the European Medicines Agency and Health Canada said last month they are considering mutual recognitions of inspections and batch certification.

The industry would also benefit from widening the scope of MRAs: for example, plasma-derived pharmaceuticals and clinical trial drugs are currently excluded from the MRAs between the FDA and European regulators, and from the MRA between the EMA and the Japanese regulator PMDA.

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*The editors of Pharmaceutical Technology*
enable these new methods to be more quickly and widely adopted.”

The fiscal year 2019 budget includes $58 million to accelerate the development of the regulatory and scientific architecture, Gottlieb wrote. In August 2018, the agency issued nearly $6 million in grants to Rutgers University, the Massachusetts Institute of Technology, and the Georgia Institute of Technology to study improvements to continuous manufacturing, monitoring, and control techniques (8). An additional $2.4 million in grants were awarded to six universities to investigate improvements to continuous manufacturing for biologic-based drugs (9).

More transparency?
Increased transparency by regulatory authorities about review and enforcement processes could inform other bio/pharma companies about potential pitfalls in development or manufacturing processes. The need for confidentiality and protection of trade secrets, however, restricts information that can be released.

FDA warning letters disclose a limited amount of information about violations. Observations reported on Form 483 documents often are not revealed. Issues noted in complete response letters are rarely publicized. And, pharma companies have released information about clinical trials that was contrary to FDA findings (10). The FDA commissioner has authority under 21 Code of Federal Regulations 20.82 to disclose records under certain circumstances, but rarely does.

More collaboration and research
Although the complexities of drug manufacturing may exceed that of other industries—including snack foods and laundry soaps—can bio/pharma learn from other industries about adopting new technologies?

“I would like to say yes, but in my experience the answer is no. The difference in how bio/pharma develops products with clinical trials and is regulated relative to most other industries makes a big difference,” said Hausner. “In other industries, it is much easier to try other technologies, but this is more costly and more risky in pharma. What results is the need for some sort of perceived advantage in order for the cost/benefit analysis to work, and this often comes in the form of regulatory acceptance, exclusivity (biosimilars), expedient (breakthrough designation), etc.”

Pre-competitive efforts have paid off in other industries, explained Carbonell. “Years ago, the microelectronics industry created large, pre-competitive non-profit consortia of manufacturers, academic and research institutions, and government agencies to evaluate new technologies, such as SEMATECH, to standardize and harmonize equipment, connectors, and measurement devices and approaches,” he said. “These efforts played a key role in reducing costs and advancing the chip manufacturing industry in the US.”

“Pre-competitive industry organizations play a major role by helping to inform the public consensus on new technology. This aids in regulatory understanding, acceptance, and approval,” said Hausner. “These groups perform a soft harmonization on technology and nomenclature ahead of more official groups like regulatory bodies and standard-setting organizations.”

“Industry-university-non profit-government consortia such as NIIMBL can play a key role in accelerating the adoption of novel manufacturing approaches. New technologies that show promise in the laboratory can be tested and de-risked in an industrial setting taking into account regulatory expectations,” said Carbonell. “These consortia reduce the costs of technology development and significantly reduce the risk to an individual company of developing a new approach that may not be approved because it is not broadly accepted.”

Contract services perspective
Contract services organizations play a key role in developing and manufacturing drugs; in 2014, the Pharma & Biopharma Outsourcing Association (PBOA) was formed to represent drug industry contract manufacturing organization/contract development and manufacturing organizations (CMO/CDMO).

“PBOA has worked with a cross-industry consortium on FDA’s Quality Metrics guidelines, providing feedback from a CMO/CDMO perspective about this well-intended but potentially damaging program,” says Gil Roth, president of PBOA0. “We’ve also worked with FDA’s serialization team and their new drug shortages task force.”

In 2019, PBOA will continue work on drug shortage issues, the implementation and rollout of the Drug Supply Chain Security Act and other regions’ serialization laws. In addition, Roth says, they plan to educate FDA about the potential drawbacks of its quality metrics program and address state and local bio/pharma laws that may impact CMO/CDMOs.

**References**

10. J. Sharfstein, et. al., Journal of Law, Medicine & Ethics, 45 (2) suppl, December 2017. **PT**
Keeping valuable employees happy—and on the job—may test bio/pharma business decisions.

The bio/pharma industry has found itself under the microscope as executives search for answers to criticisms about high drug prices, shortages of vital therapies, and the industry’s role in the opioid epidemic. Meanwhile, a record number of new drug approvals and the emergence of innovative therapies demonstrate the potential of bio/pharma R&D efforts.

Bio/pharma development and manufacturing relies on skilled and knowledgeable workers. Hiring and retaining this expertise should be a top priority. With the unemployment rate at record lows, career opportunities for US-based bio/pharma employees should be promising. Insight provided by respondents to Pharmaceutical Technology’s annual employment survey (1) suggests that employee satisfaction is tied to the challenges presented by the work and the employer’s potential for success. (See the infographic on pages 26–27 for an overview of survey results.)

Salary ranked ninth on a list of 12 factors contributing to job satisfaction. Intellectual stimulation and challenging projects were the top “main reasons I come to work,” followed by supportive management, the company’s potential for success, a good work/life balance, relationships with colleagues, job security, and tolerance and opportunity for all employees. Employees based in Europe placed more emphasis on intellectual stimulation and challenging work, compared with all respondents. North America-based workers leaned more toward salary and benefits factors than the Europe-based peers.

Nearly 80% of all respondents, however, said that short timelines and insufficient budgets and resources to accomplish a task contributed to job dissatisfaction. Nearly 70% voiced “issues with management” as a source of dissatisfaction.

**Intellectual stimulation was a leading reason people go to work.**

**Respondent profile**

More than 335 bio/pharma professionals from around the world responded to the survey, which was fielded in November and December 2018. Respondents primarily were full-time, permanent employees (87.3% of respondents) at innovator bio/pharmaceutical companies (29.5%), generic-drug manufacturing companies (17.9%), and contract research and manufacturing organizations (16.7%).

The represented companies develop or manufacture both small- and large-molecule drugs (48.1%), small-molecule drugs only (28.7%), biologic-based drugs only (5.2%), vaccines (3.1%), and cell therapy or gene therapies (2.1%).

Respondents reported a range of job responsibilities including formulation, quality control/assurance, R&D, analytical studies, process development, validation, drug delivery, and manufacturing. More than 41% of respondents work for companies with more than 1000 employees; more than 49% work for companies with fewer than 500 employees.

Nearly 40% of the respondents held doctorate or higher degree; one-third held at least a Master’s degree. Compared with previous years, the respondents reported more experience working in the bio/pharma industry; 21.9% had fewer than 10 years of experience, 24% had 10–20 years, 42.4% had 20–35 years of experience, and 11.8% have worked in the industry for more than 35 years.

Text contin. on page 28
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<table>
<thead>
<tr>
<th>Perception</th>
<th>2018</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>I am paid below market value, considering my level of expertise and responsibility.</td>
<td>20.5%</td>
<td>18.7%</td>
</tr>
<tr>
<td>I am paid within market value for my job function, but at the low end of the range, considering my level of expertise and responsibility.</td>
<td>38.2%</td>
<td>35.3%</td>
</tr>
<tr>
<td>I am paid fairly for my level of expertise and responsibility.</td>
<td>39.2%</td>
<td>43.6%</td>
</tr>
<tr>
<td>I am paid excessively for my level of expertise and responsibility.</td>
<td>2.1%</td>
<td>2.3%</td>
</tr>
</tbody>
</table>
Bio/pharma workers contemplate job and career changes.

What is your prediction for your company’s business prospects in the coming year?

- **Global**
  - Improve: 21.9%
  - Decline: 17.7%
  - No Change: 38.1%

- **Europe**
  - Improve: 21.9%
  - Decline: 20.3%
  - No Change: 34.5%

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

<table>
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<tr>
<th></th>
<th>2018</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>It would be straightforward to find a job comparable to the one I have now.</td>
<td>27.4%</td>
<td>25.8%</td>
</tr>
<tr>
<td>It would take a while, but I would be able to find a job comparable to the one I have now.</td>
<td>44.3%</td>
<td>44.4%</td>
</tr>
<tr>
<td>It would be straightforward to find a job, but it probably wouldn’t be as good as the one I have now.</td>
<td>12.7%</td>
<td>14.8%</td>
</tr>
<tr>
<td>I would have to search hard and be prepared to take what I could get.</td>
<td>15.6%</td>
<td>15.1%</td>
</tr>
</tbody>
</table>

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

- Less than 2 years: 17.2%
- 3 to 5 years: 22.7%
- 6 to 10 years: 30.2%
- 11 to 20 years: 21.1%
- More than 20 years: 3.6%
Competition for open positions is strong.
Employers compete for qualified candidates.

Which statement best describes the job market for scientific or technical positions in bio/pharmaceutical development and manufacturing in your geographic area?

- Competition for open positions is strong.
- Employment competition is moderate.
- Employers compete for qualified candidates.

Salary was the third most cited reason for job change, trailing professional advancement and intellectual challenge. Job security and scientific opportunities were other leading reasons noted.

Most respondents were confident they would be able to secure a job comparable to the one they currently hold; 27.4% said it would be straightforward to find a new position; 44.3% said the search would take a while.

 Respondents were divided almost evenly when assessing the pool of qualified candidates and available job openings; 30.3% said there are few qualified candidates for open scientific/technical positions, 34.2% said there were more qualified candidates than open positions, and 35.6% said there was moderate competition for open positions. Respondents were not impressed by the skill sets or knowledge of new hires for their job function; 75.2% said the new hires were adequately trained but not exceptional; 17.8% said they were poorly trained.

Respondents reported a slight increase in employer-provided training for basic skills compared with previous years; however, training for advanced functions declined slightly.

Geography influences employment security and business outlook
Respondents were split on job security. Almost one-quarter of respondents said they felt more secure in their position compared with the previous year; only 19.1% felt more secure in 2017. However, 30.6% of all respondents said they were less secure, compared with 27.8% who said they felt less secure in 2017.

Geographic differences, and perhaps uncertainty created by Brexit, resulted in a more negative outlook for business prospects by European-based respondents. While 52.7% of all respondents expect business to improve, fewer than 40% of European-based respondents had a positive outlook. Nearly one-quarter (22.7%) of the Europe-based respondents expect business to decline; 37.9% expect no significant change. In comparison, 17.2% of all respondents project business will decline; 30.2% expect no significant change.

In the past two years, nearly one-third of the respondents reported that their companies had been through a downsizing or restructuring, and 18.1% experienced a merger or acquisition. Nearly 40% reported a change in responsibilities due to the changes in company structure. Only 10% said they left the company due to an acquisition, downsizing, or restructuring.

One-quarter of the respondents said they voluntarily changed jobs in the past two years; among the reasons cited—with multiple choices allowed—were to pursue a better career opportunity (48.7%), find more challenging work (31.1%), or to seek a better work-life balance (20.3%).

References
1. 2018 Pharmaceutical Technology/Pharma
2. 2017 Pharmaceutical Technology/Pharma
caceutical Technology Europe Employment Survey, Pharmaceutical Technology, 2017. PT
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In 2018, FDA had a very active year. The agency investigated ways to improve the drug approval process, increase the efficiency of drug development and better incorporate patient voices in the process, increase access for the public to less expensive generics, and develop solutions for the prevention of drug shortages.

Reorganization and new guidance
In June 2018, FDA Commissioner Scott Gottlieb issued a statement about a proposal to modernize the agency’s drug review office (1). The proposed changes at the Office of New Drugs in the Center for Drug Evaluation and Research (CDER) were intended to provide its “clinicians and scientists more time, better tools, and greater support to advance the clinical and regulatory principles that the FDA uses to evaluate new drugs for safety and efficacy.”

Also in June, FDA issued the first of four draft guidance documents intended to inform patients and product developers about rigorous approaches for obtaining and incorporating patient input in product development and how the agency will incorporate this information into its regulatory decision-making (2).

To speed drug development, FDA announced in October 2018 that the agency is developing technology- and disease-specific regulatory frameworks for innovations that may not have previously had a clear development pathway, including modernization of the agency’s approach to clinical trial design (3). It also issued several guidance documents for newer trial designs and the development of next-generation therapies.

These changes may have helped—or certainly not hindered—the ability of the agency to review new drug applications. In 2018, CDER had approved 59 novel drugs (4), 13 more than approved in 2017 (5). The following information was sourced from press releases issued by FDA and the drug license holders. Links to references and a list of 2018 drug approvals are published online on www.PharmTech.com/pt/2018approvals.

Many accelerated drug approvals
Based on information in FDA and company press releases, approximately half of the new drugs were approved under an expedited review process—Fast Track, Breakthrough Therapy, Priority Review, Accelerated Review—or orphan drug status. These results suggest that both pharma companies and FDA remain committed to leveraging the shorter approval pathways made possible in the 2012 Food and Drug Administration Safety Innovations Act.

Nearly one-third of the new drugs were granted orphan drug designation, clearly reflecting the shift taking place in the industry away from the development of blockbuster drugs to the development of therapies for rare diseases.

Despite all of the hype about and investment in biologic drugs, only one quarter of medicines approved in 2018 by FDA were biologic-based drugs.

New ways to fight infections
In response to concerns about the growing prevalence of drug-resistant bacteria and the ongoing need for medications to treat a variety of infections, FDA has placed an emphasis on approving new antibiotics and antivirals.

Paratek Pharmaceuticals received approval for its modernized tetracycline antibiotic Nuzyra (omadacycline) for the treatment of adults with community-acquired bacterial pneumonia and acute skin and skin structure infections. Nuzyra is specifically designed to overcome tetracycline resistance and exhibits broad-spectrum activity. It is also the first and only once-daily intravenous (IV) and oral antibiotic approved for the treatment of both types of infections. Its use enables physicians to transition patients from IV to oral treatment and potentially reduce hospitalizations. Xerava (eravacycline) from Tetraphase Pharmaceuticals is a novel, broad-spectrum antibiotic approved for the treatment of complicated intra-abdominal infec-
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tions, the most common infection site in intensive care units.

New antiviral medications approved in 2018 include Shionogi’s Xofluza (baloxavir marboxil) for the treatment of acute uncomplicated influenza (flu), the first new antiviral flu treatment with a novel mechanism of action approved by FDA in nearly 20 years, and Tpoxx (tecovirimat), the first drug approved for the treatment of smallpox. Tpoxx was developed by SIGA Technologies in conjunction with the US Department of Health and Human Services’ Biomedical Advanced Research and Development Authority; SIGA received a Material Threat Medical Countermeasure Priority Review Voucher.

Four new treatments for HIV patients were also approved by FDA in 2018. Biktaresv (bictegravir 50mg/emtricitabine 200mg/tenofovir alafenamide 25mg, BIC/FTC/TAF) from Gilead Sciences is a once-daily single tablet regimen for the treatment of HIV-1 infection; Trogazer (ibalizumab--uiyk) from TaiMed Biologics is the first drug in a new class of antiretroviral medications that can provide significant benefit to patients who have run out of HIV treatment options. Merck’s Delstrigo (darovirine/lamivudine/tenofovir disoproxil fumarate) is a once-daily fixed-dose combination tablet, and Pifeltro (darovirine) is a new non-nucleoside reverse transcriptase inhibitor; both were developed for the treatment of HIV-1 infection in adult patients with no prior antiretroviral treatment experience.

**First drugs for rare diseases**

Treatments for rare genetic diseases, all with the orphan drug designation, received approval by FDA. Onpattro (patisiran) infusion from Alnylam Pharmaceuticals is the first FDA-approved treatment for patients with polyneuropathy caused by hATTR and is the first in a new class of drugs referred to as small interfering ribonucleic acid treatments. Akcea Therapeutics’ Tegsedi (inotersen), also for the treatment of the polyneuropathy of hereditary transthyretin–mediated amyloidosis in adults, is the first RNA-targeting therapeutic designed to reduce the production of human transthyretin protein.

Takhzyro (lanadelumab) from Shire is a plasma kallikrein inhibitor and the first monoclonal antibody (mAb) approved in the United States to treat patients 12 years and older with types I and II hereditary angioedema, a rare and serious genetic disease that leads to unpredictable episodes of severe swelling in different areas of the body. Dompé farmaceutici’s Oxervate (ce- negermin) is the first drug approved by FDA for the treatment of neurotrophic keratitis, a rare disease affecting the cornea, providing an alternative to surgical intervention.

Galafold (migalastat) from Amicus Therapeutics is the first oral medication for the treatment of adults with Fabry disease and specifically for patients who have a genetic mutation determined to be responsive to treatment with Galafold based on laboratory data. Unlike enzyme replacement therapy, this drug increases the activity of the body’s deficient enzyme.

Crysvita (burosumab-twza) is the first drug approved for the treatment of x-linked hypophosphatemia, a rare, inherited form of rickets that does not respond to vitamin D therapy; Ultragenyx Pharmaceutical received the 14th Rare Pediatric Disease Priority Review Voucher awarded by FDA. Palynziq (pegvaliase-pqpz) from BioMarin Pharmaceutical is a novel enzyme therapy approved for the treatment of adult patients with phenylketonuria, a rare genetic disease, who have uncontrolled concentrations of phenylalanine in their blood even on current treatment.

**New cancer treatments**

Treatments for both common and rare cancers were approved by FDA in 2018, including Regeneron Pharmaceuticals’ PD-1 checkpoint inhibitor Libtayo (cemiplimab-rwlc) injection, the first approved treatment for metastatic or locally advanced cutaneous squamous cell carcinoma, the second most common skin cancer. Lumoxiti (moxetumomab pasudotox-tdfk) injection from AstraZeneca Pharmaceuticals is the first CD22-directed cytotoxin approved for the treatment of adult patients with relapsed or refractory hairy cell leukemia who have received at least two prior systemic therapies, including treatment with a purine nucleoside analog. Kyowa Kirin’s Potelogo (mogamulizumab-kpc) injection is the first drug approved by FDA for the treatment of Sézary syndrome, a rare and hard-to-treat type of non-Hodgkin lymphoma.

Erleada (apalutamide) from Janssen Pharmaceutical Companies is the first FDA-approved treatment for non-metastatic, castration-resistant prostate cancer. The approval was the first to use the endpoint of metastasis-free survival, measuring the length of time that tumors did not spread to other parts of the body or that death occurred after starting treatment. It was the first participant in FDA’s Clinical Data Summary Pilot Program, an effort to provide stakeholders with more usable information on the clinical evidence supporting drug product approvals.

Lutathera (lutetium Lu 177 dotatate) from Advanced Accelerator Applications (since acquired by Novartis) is the first radiotherapy approved for the treatment of gastroenteropancreatic neuroendocrine tumors, which affect the pancreas or gastrointestinal tract. The drug binds to the somatostatin receptors of tumor cells, enabling its entry and their ultimate destruction.

In late November, FDA approved Vitraitki (larotrectinib) from Loxo Oncology for the treatment of adult and pediatric cancer patients with a specific genetic feature, or biomarker, on their tumors. The approval marks the second time FDA has approved a cancer treatment based on a common biomarker across different types of tumors rather than the location in the body where the tumor originated.

**Other firsts**

Several other firsts were achieved by FDA in 2018. Approval of the first non-opioid treatment for the management of opioid
withdrawal symptoms went to US WorldMeds’ Lucemyra (lofexidine hydrochloride), an oral, selective alpha 2-adrenergic receptor agonist that reduces the release of norepinephrine. Epidiolex (cannabidiol) from GW Research for the treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome, two rare and severe forms of epilepsy, is the first FDA-approved drug that contains a purified drug substance derived from marijuana and the first drug approved for the treatment of patients with Dravet syndrome.

AbbVie’s Orilissa (elagolix) is the first FDA-approved oral treatment for the management of moderate to severe pain associated with endometriosis in over a decade, and the only oral gonadotropin-releasing hormone antagonist specifically developed for women with moderate to severe endometriosis pain.

FDA also approved new medications for the prevention of migraines. Aimovig (erenumab-aooe) from Amgen is a once-monthly self-injection for the prevention of migraines in a new class of drugs that work by blocking the activity of calcitonin gene-related peptide. Teva Pharmaceutical Industries’ Ajovy (fremanezumab-vfrm) injection is the first and only anti-CGRP treatment for the prevention of migraine with quarterly and monthly dosing options. Eli Lilly’s Emgality (galcanezumab-gnlm) also received approval.

Targeted therapies, diagnostic tests
Several drugs that received FDA approval in 2018 were targeted therapies, and some were even approved with specific diagnostic tests. Pfizer’s Talzenna (talazoparib), a poly (ADP-ribose) polymerase (PARP) inhibitor, was approved for the treatment of patients with deleterious or suspected deleterious germline BRCA-mutated, HER2 negative locally advanced or metastatic breast cancer. The BRACANalysis CDx test from Myriad Genetic Laboratories, Inc. was also approved to identify patients who are eligible for the new drug.

Agios Pharmaceuticals received approval for Tibsovo (ivosidenib), the first isocitrate dehydrogenase-1 inhibitor, for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) who have a specific genetic mutation. Patients must be identified using the FDA-approved RealTime IDH1 Assay from Abbott Laboratories.

The combination of BRAFTOVI (encorafenib) and MEKTOVI (binimetinib) from Array BioPharma was approved for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation. The mutation must be detected using the FDA-approved THXID BRAF Kit from bioMérieux.

New development paradigms
One interesting trend is the development of new drugs by non-profit organizations, sometimes in collaboration with pharmaceutical companies. Two drugs approved to treat tropical diseases were developed using this approach. The not-for-profit company Medicines Development for Global Health (MDGH), in collaboration with the World Health Organization Special Program for Research and Training in Tropical Diseases, received FDA approval for moxidectin 8 mg oral for the treatment of river blindness, which is caused by the parasite Onchocerca volvulus. It is the first new drug approved for the treatment of river blindness in 20 years. MDGH received a priority review voucher (PRV), a saleable item that enables the owner to receive accelerated review of a new drug application (NDA)—the first not-for-profit company to do so under the tropical disease PRV program.

Similarly, GlaxoSmithKline (GSK) received a tropical disease PRV for its part in the development of the first new treatment for Plasmodium vivax (P. vivax) malaria in patients aged 16 years and older who are receiving appropriate antimalarial therapy for acute P. vivax infection.

Two other interesting examples are the first approval of a vaginal ring contraceptive: the Population Council’s Annovera (segesterone acetate and ethinyl estradiol vaginal system); and Omegaven, a fat emulsion manufactured by Fresenius Kabi and demonstrated by researchers at Boston Children’s Hospital to be effective for preventing liver disease associated with parenteral nutrition in children.

In the approval pipeline
Most of the drugs on FDA’s approval docket through early 2019 include treatments for many common conditions, including heart disease, immune deficiency, diabetes, and influenza. There are also several treatments for neurological and psychological disorders, such as Parkinson’s disease and depression. Several drugs for pain management are under review, as are treatments for skin infections, glaucoma, breast cancer, and erectile dysfunction. Several new drugs for the treatment of rare cancers are also awaiting FDA decisions.

References
New approaches seek to address formulation and delivery challenges for these complex molecules.

Since the first recombinant protein therapeutic, human insulin, was approved by FDA in the early 1980s (1), there have been significant advances in the biopharmaceutical market. The industry is currently witnessing the emergence of protein and peptide therapeutics across a multitude of indications, such as oncology, infectious diseases, endocrinology, and immunology. The high selectivity and specificity of these macromolecules offer increased treatment efficacy while also potentially reducing the side effects and toxicity that are sometimes present with alternative therapeutic options (2).

“There is enormous therapeutic potential in proteins and peptides,” says Rashmi Nair, senior scientist, Formulations at Dr Reddy’s. “Major benefits that they offer over conventional small molecules could be attributed to their structural and functional similarities to endogenous biochemicals in the human body. This similarity translates into better drug targeting, lesser side effects, and new treatment options for various diseases where complex chemistry is restricted in small molecules.”

Susanne Joerg, head of formulation development, Drug Product Services, Lonza Pharma & Biotech adds, “Protein and peptide therapeutics have the potential to provide safer and more targeted therapies. They consist of amino acids and can interact with target receptors or ligands to convey their pharmacologic action. As they specifically have the potential of a more targeted interaction with receptors or ligands, they thus have a lower risk for off-target toxicity, a characteristic of many chemical molecules. An example is chemotherapy agents (such as cisplatin) being used for cancer treatment, versus targeted antibodies that block and prevent specific cell growth.”

Yet, despite the therapeutic advantages these macromolecules offer, they are also associated with several notable disadvantages, such as limited bioavailability as well as physical and chemical instability. These disadvantages have proven problematic for developers looking to create the best formulation and delivery method for these compounds and have limited their use.

**Formulation and delivery: Challenges to success**

As reported by Cleland and Langer more than 20 years ago, “The success of most peptide and protein drugs is dependent upon the delivery of the biologically active form to the site of action” (3). To achieve this, Cleland and Langer stressed that developing the most stable formulation possible is a requirement, and consideration of multiple routes of administration is important for future formulation development (3).

**Production considerations.** Producing protein or peptide therapeutics is highly complex and can include many more critical process steps than those required for a small-molecule drug (4). Additionally, manufacturers typically use living cells or organisms to synthesize the macromolecules, which can impact the characteristics of the final product (4). Research into protein-engineering strategies during drug development aims to address complex manufacturing processes (4).

“Structural modification with PE-Gylation, cyclization, chemical conjugation, use of enzyme inhibitors, absorption enhancers, encapsulated carriers, and so on, are all being employed to address the challenges of stability and delivery of protein and peptide therapeutics,” adds Nair. “A
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combination of approaches is often required that takes into consideration the route of administration and required target bioavailability.”

Direct structural modification, such as cyclization, PEGylation, and chemical conjugation, are considered to be key strategies in improving bioavailability and stability of peptide therapeutics (5). Co-administration techniques, such as with enzyme inhibitors, absorption enhancers, and encapsulated carriers are being assessed to improve the ability to deliver the macromolecules.

For Joerg, the most appropriate formulation development is vital in overcoming stability issues with these complex drug products for parenteral administration. “While freeze-drying usually provides the best stability, liquid dosage forms are preferred due to lower complexity for use and administration,” she says.

“To ensure appropriate product quality during manufacturing, integrated approaches for drug substance and drug product processing are critical, including the evaluation of ultrafiltration/diafiltration approaches, the composition of drug substance and product, and thorough evaluation of all drug substance and drug product manufacturing unit operations and operating ranges,” Joerg continues. “For example, the choice of a wrong fill pump can render a whole batch of protein product instable and non-compliant.”

**Administration route considerations.**

Drug delivery challenges posed by protein and peptide therapeutics are many. Not only are the molecules large in size but they are hydrophilic, cannot easily cross biological barriers, are degraded by enzymes, rapidly leave the circulation system, and are highly charged, all of which complicate the delivery strategy. Commonly, as a result of these challenges, parenteral formulations and routes of administration have generally been the ‘go-to’ for these promising therapeutic options.

“Two major drug delivery routes are oral and parenteral,” states Nair. “While parenteral delivery is more commonly used, it has its own challenges with a short half-life of the drug resulting in frequent drug dosing and eventually less patient compliance.”

Joerg adds, “The size and hydrophilicity of proteins make it difficult to achieve sufficiently large and robust bioavailability without parenteral administration, which includes intravenous, intra-arterial, subcutaneous, intramuscular, intra-thecal, and intravitreal/intraocular administration. All these routes of administration have specific challenges in terms of allowed volume for administration, pH, and osmolarity requirements, and, of course, all parenteral preparations must be sterile and compliant with regards to endotoxin and particle requirements, for example.”

Low bioavailability and metabolic liability have also limited the oral administration of protein and peptide therapeutics (5–7). “Proteins and peptides do not sustain the rigor of the gastrointestinal tract. Chemical degradation in gastric fluids, extensive metabolism in luminal spaces, and first pass metabolism are major concerns with oral delivery of proteins and peptides,” says Nair.

However, oral delivery is considered to be the preferred route of administration due to the benefits it offers—patient convenience and acceptance, which in turn leads to increased patient compliance (6,7). “Even in the few examples where peptides have sufficient bioavailability after oral or inhalation administration for systemic use, there are various other challenges to be managed and overcome, such as cost-of-goods, safety, or toxicity of the compounds and variability in patients,” continues Joerg. “The numerous attempts to try and overcome parenteral administration have seen very limited success—primarily due to the inherent complexity of structure, hydrophilicity of the molecule, and the fact that our bodies have been designed to digest proteins through the oral route.”

Yet, she notes an advance in a more patient-centric approach to delivery that has been garnering increasing attention lately is the use of autoinjectors, syringes, or pens as delivery devices. “For example, monoclonal antibody therapies for subcutaneous administration often are used with syringes or even large-volume patch pump devices,” she adds. These techniques, along with improved focus on formulation evaluation and using a more systemic approach of following quality by design for process unit operations, are all helping to progress delivery, she further explains.

“However, appropriate product design and thorough planning of clinical (or patient) use, adequate in-use testing, and instructions for use (IFUs) are of utmost importance,” Joerg cautions. “For example, syringes and autoinjector systems can often facilitate self-injections of patients. But, a properly designed IFU and appropriate training of the patient is required to ensure compliance.”

**A multidisciplinary approach needed for the future.**

Over the past 30 years, there has been extensive research into improving the stability and delivery of protein and peptide therapeutics. The success of this work is being reflected in the fact that increasing numbers of these therapies are being approved by regulatory bodies (8) and, in terms of delivery, the growth of the oral peptides and proteins market (9).

In the near future, Joerg anticipates that more attention will be put on the integrated development of the drug substance and product and more systemic evaluations of all parameters. “There is an increasingly considerable demand coming from the industry for an integrated solution from a sole vendor who has a combination of scientific and regulatory experience,” she says. “As we
see pipelines moving to progressively complex biologics—for example, antibody drug conjugates, bispecific antibodies, fusion proteins, and other second-generation antibody therapies—the question of drug product becomes even more pertinent. Many companies are therefore looking for expertise that they may not have internally to solve these challenges.”

In terms of drug delivery, Joerg notes that, even though there have been numerous attempts at progressing alternatives to parenteral administration, injections or infusions remain, at this moment in time, the primary option. “In order to facilitate administration, devices will play a key role,” she continues, “with increasing connectivity to the Internet of things.”

For Nair, the past decade has been particularly encouraging for proteins and peptides. “Many new drug design tools, in-silico screening software, and predictive simulations have helped drug development programs. Stably folded, cell-penetrating proteins and peptides have advanced in clinical studies. Carrier-mediated drug delivery with microspheres and liposomes has enabled the commercialization of many promising drugs,” she adds.

In the coming decade, Nair predicts that there will be more development into the use of polymers for drug delivery, which could protect proteins and peptides from physical and chemical degradation and also help to sustain the drug release profile through depots or prolonged blood circulation times. “But, an important point,” Nair concludes, “is the consideration of integrated drug substance and drug product projects in drug development programs. Through this, overcoming the challenges of protein and peptide drug delivery will be increased as this is essentially a multidisciplinary science that requires an understanding of organic chemistry, biochemistry, pharmaceutical technology, and physical chemistry.”

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Continuous Processing: Challenges and Opportunities of Virus Filtration

Birte Kleindienst, Peter Kosiol, and Anika Manzke

Bioprocessing technologies have evolved rapidly and significantly during the three decades the biopharmaceutical sector has been in existence. Despite the success of operational improvement programs and measurable increases in productivity, biomanufacturing continues to face challenges (1). Increased cost, quality and production pressures, oncoming competition from biosimilars, and the growing importance of emerging markets and personalized medicines are creating the need for further evolution in bioprocessing technologies (2, 3).

Steady-state conditions with continuous process approaches have been introduced to decrease cycle times, reduce capital and operating costs, and enable faster scale-up with more consistent quality and greater manufacturing flexibility (3, 4). At this point, end-to-end, fully integrated continuous processing has not been implemented outside the laboratory. Solutions are still being investigated for realizing enclosed, bioburden-free, fully automated, fully continuous processes from bioreactor to formulated drug product with global process control that run for long durations (1, 2). In the meantime, hybrid or semi-continuous approaches are being implemented by early adopters of continuous bioprocessing.

Batch vs. continuous virus filtration

Virus filtration is a crucial downstream processing operation that must be carefully considered when implementing continuous bioprocesses to ensure patient safety. There are several differences between batch and continuous virus filtration process parameters. The unit operations in batch mode typically last for four to six hours, while continuous processes can be performed for days. Operating pressures are also much lower during continuous virus filtration, and an adsorptive pre-filter is essential for the removal of potential aggregates that might lead to fouling of the virus filter. Batch systems are open with manual or semi-automated control, while continuous processes are closed, more complex, and highly automated. The feedstream for a batch process is homogeneous, but in continuous virus filtration, variability in protein concentration, pH, and conductivity from the elution peaks of the previous chromatography step will challenge the virus filter (1).

Design space of continuous viral filtration

In batch processing, it is known that protein concentration, pH, conductivity, buffer type, viscosity, additives, operating pressure, and pressure release times can affect virus filter performance. The question is: which of these process variabilities are relevant for continuous virus filtration? To begin answering this question, a design-of-experiment (DoE) study was conducted to define the design space for continuous virus filtration. A full factorial DoE ($2^3$) was performed including a total of 10 experiments that varied the length of the run, the operating pressure, and either a monoclonal antibody (mAb) or buffer feed. Depending on the total length of each run, pressure was applied for 24 or 48 hours twice with a 30-minute pressure release after each filtration period as shown in Figure 1. For the 48-hour runs, an additional pressure release of 60-minutes was conducted. Fractions were collected in the beginning of each filtration and before and after each filtration period and pressure release to evaluate any impacts of the pressure profile.

Filtration parameters. Because continuous virus filtration is operated at much...
lower flow rates, longer filtration times often involve longer pressure releases than are observed with batch filtration; these operating parameters were included in the DoE study. Although continuous filtration is typically run at constant flow rather than constant pressure, for ease of experimentation, a constant pressure range of 0.1 bar (1.5 psi) up to 0.5 bar (7.2 psi) was covered to represent a maximum of 25% of the flow used in batch operations at 2.0 bar (30 psi). Filtration times of 48 to 96 hours were used to keep the operating time within the normal five-day work week.

**Virus model.** *Pseudomonas aeruginosa* bacteriophage PP7 (ATCC 15692-B2), a single stranded, 20–25 nm, non-enveloped, ssRNA bacteriophage from the Leiviviridae family, was used. PP7 bacteriophage is an established model system that is often used to evaluate the removal capabilities of virus filters (5). The filters were challenged with a minimum titer of 10\(^6\) pfu/mL.

**Product feed.** A mAb feed (non-optimized after ion exchange chromatography at 0.3 g/L in 20 mM, pH 7.2 TRIS hydrochloric acid and 150 mM sodium chloride) and a buffer solution (20 mM KPI buffer, pH 7.2) were used to test virus retention in the presence and absence of protein to exclude the possibility of interactions between the mAb, the PP7, and the virus retentive membrane (commercial, down-scaled 1.7 cm\(^2\) Virosart HF filter with a down-scaled 5.0 cm\(^2\) Virosart Max adsorptive 0.1 μm inline pre-filter, both from Sartorius Stedm Biotech). It was determined upfront that the pre-filter did not remove bacteriophage PP7 in a significant amount.

**Results.** Results for the DoE study using the buffer and mAb feed are shown in **Figure 2**. Notably, in both cases, retention without any virus breakthrough was achieved over the entire filtration period for each experiment. Therefore, a robust log\(_{10}\) reduction value (LRV) of greater than four was achieved independent of operating pressure, pressure release time, and overall filtration time. The titer of PP7 bacteriophages declined over the course of 96 hours from 10\(^6\) down to 10\(^5\) pfu/mL, whereas the mAb feed seemed to stabilize the titer.

Separately, the stability of typical model viruses used for validation studies of virus filters was investigated under the long processing time present in continuous manufacturing. Simple infectivity tests were conducted for Minute virus of mice (MVM) and Murine leukemia virus (MuLV) in the buffer and mAb feed used for the DoE study. The results over 96 hours are shown in **Figure 3**.

MVM and MuLV infectivity decreased during the 96-h operation time. The decline in MVM infectivity of 0.5 LRV is within the variation of the assay. MuLV, a large enveloped virus known to be a less stable virus, showed a higher decrease of titer with 1 LRV.

**Virus clearance validation**

New ways of manufacturing, such as continuous processing, bring up new challenges for process validation. A representative feedstream for the virus validation studies needs to be defined. In addition, while the DoE results presented here indicate that filtration parameters do not have a significant impact on virus retention, such performance must be confirmed by end users under their specific process conditions. One possible approach is to conduct a DoE type of validation by identifying the critical parameters (e.g., concentration, flow, pH, conductivity) and then validating only the representative worst-case conditions.

The manner in which the virus should be spiked has also to be addressed. Typically, in batch processing, the “spike and
run” method is used, in which the spike is added to the pooled feedstream prior to the virus filtration. This approach is difficult to realize with a continuous flow of product. Inline spiking for continuous dosing into the feed seems to be the most likely workable approach in the industry. This method can overcome the challenges of loss virus infectivity over time because fresh virus can be continuously introduced. Inline spiking involves a complex setup and equipment, however.

Numerous other challenges for validation of continuous virus filtration must be addressed, such as the use of an inline pre-filter and potential filter blockage by the feedstream and/or virus itself with increasing volume.

**Process implementation**

One possible process implementation for virus filtration in continuous processing is to use a set-up with two filtration lines that can be operated independently of each other in a preparation mode or operation mode (2, 6), as shown in Figure 4. Each line has a pump, flow and pressure sensor, adsorptive pre-filter, virus filter, and buffer and water-for-injection supply. Steps such as flushing, equilibration, filtration, buffer flush, wetting for integrity tests (IT), and IT are performed in preparation mode, whereas the product filtration is performed in operation mode. Ideally all valves would be fully automated, and implementation would be achieved in a sterile manner to avoid the need for steam-in-place and clean-in-place operations.

Passed IT of virus filters are essential in order to release a batch, which is a challenge in continuous processing (7). Risk assessments have to be performed in order to minimize the risk of failed post-use IT in production. Some potential approaches like conducting pre-use, post-sterilization IT (PUPSIT) on all filters are currently discussed in the industry to mitigating the risk. This approach could potentially be incorporated into an end-to-end, integrated continuous process from bioreactor to fill/finish.

**Conclusion**

In this study, the design space for continuous virus filtration was defined with respect to filtration parameters, and parameters such as low flow rates, long filtration times, and increased pressure releases showed no impact on the filter tested. Commercially available virus filters can be run in continuous mode. Although some challenges for validation of continuous virus filtration must still be addressed, parallel filtration lines that allow in-line filter testing are one concept for allowing implementation of continuous virus filtration in commercial manufacturing.

**Acknowledgements**

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**References**


Soft gelatin capsules (SGC) are popularly used pharmaceutical dosage forms, whose critical quality attributes are efficient opening/rupture, disintegration, and dissolution. Unlike oral capsules, however, rectal capsules must dissolve in minimal fluid and hydrodynamics, without digestive enzymes to break down the crosslinking of gelatin, if any. Therefore, a reliable biomimetic method is needed to characterize SGC rupture/disintegration during rectal administration. This article demonstrates how qualitative physical attributes testing, a method that has recently been approved for use by the World Health Organization, can be used to achieve these goals.

Soft gelatin capsules (SGC) are popularly used pharmaceutical dosage forms, wherein the active ingredient is delivered in a non-aqueous vehicle, either as solution, suspension, or semisolid, through various routes of administration. SGC offers unique advantages of filling high doses of poorly water-soluble drugs, loading of ultra-low dose drugs accurately (e.g., cardiac glycosides and vitamin D analogs), and providing the option of filling excipients that inhibit P-glycoprotein for better bioavailability (1).

Quality control of SGC is crucial to ensure the product’s intended in-vivo performance, and a variety of quality control tests are available to use for evaluation (2, 3). The critical quality attributes are efficient opening/rupture, disintegration, and appropriate dissolution in biological fluid.

Table I (4,5,6) lists methods that assess the disintegration or rupture of SGCs. However, these tests are best suited to orally administered SGCs because they require a large volume of fluid (e.g., 500 mL). Rectal SCGs are exposed to very different conditions (i.e., limited fluid volume [7] and hydrodynamics). Hence, a suitable test that is biorelevant in terms of media, volume, hydrodynamics, and capability to quantify the disintegration or rupture events of SGC for rectal use is essential.

Artesunate SGCs were developed as a pre-referral treatment option for malarial infection in children under six years of age living in remote tropical areas with limited access and to provide a standard care of treatment (intramuscular artesunate) in hospitals (8). Suppositories hold an advantage over oral therapy when treating severely ill children who are vomiting and who may be weak or losing consciousness, because they act faster than the oral dosage forms.

The authors tested a new apparatus and method, termed qualitative physical attributes testing (QPAT), which was developed to address this need. The results of the test using artesunate SGCs are summarized in this article.

Materials and methods
Materials. For buffer preparation, potassium dihydrogen phosphate (analytical reagent [AR] grade, S.D.Fine Chem), sodium hydroxide (AR grade, S.D.Fine Chem), orthophos-
phoric acid (laboratory reagent (LR) grade, Rankem), cetyltrimethyl ammonium bromide (CTAB) (extrapure AR grade, Sisco Research Laboratories), and purified water were used.

**Preparation of buffer medium.** The buffer solution used as the medium for the QPAT study was prepared by dissolving potassium dihydrogen phosphate and sodium hydroxide in purified water, to which a suitable quantity of CTAB was added to prepare phosphate buffer (pH 7.2, 1.5% CTAB).

**Equipment (prototype).** The researchers assembled a temperature-controlled glass water bath that consisted of an appropriate cylindrical glass-holding tube (vessel) capable of holding 10 mL or less of selected medium with controlled hydrodynamics and a platform (stainless steel mesh screen) to support the unit dosage form. The glass container had an opening with the required diameter to facilitate the introduction of the unit sample (one rectal SGC). The water bath could hold three glass containers, which facilitated QPAT of three units individually and simultaneously. Additionally, the glass assembly facilitated visual observation of the physical events that each unit dosage form was undergoing during the duration of QPAT. The hydrodynamics of the water bath and medium in the holding tube were controlled by appropriately sized bar magnets in the respective chambers. The whole setup was placed on a magnetic stirrer with hotplate.  

**Experimental procedure.** The critical steps of the experiment are described below. These steps will ensure reproducibility and accuracy of experimentation and measurements:

- A large bar magnet was placed at the bottom of the outer water bath.
- The water bath was filled with water to the specified depth at room temperature and placed on a magnetic stirrer with hot plate and heated to 37±2 °C.
- Three cylindrical glass-holding tubes were lowered into the water bath and positioned at specified height.
- A small bar magnet was placed at the bottom of each of the cylindrical glass holding tube.
- Stainless steel mesh screen was placed in each of the cylindrical glass holding tube.
- A suitable volume (10 mL or less) of medium was poured into each of the cylindrical glass holding tube.
- Rotations for the bar magnet were started at the specified settings.
- Temperatures in the outer water bath and the cylindrical glass holding tube were recorded until the temperature was stable at 37±2 °C for at least 5 min.
- One dosage unit (artesunate SGC) was introduced into each of the cylindrical glass holding tube.
- The time was noted and designated as T=0 min.
- Physical behavior of the dosage unit was observed for any changes (not in any order of significance), such as physical disintegration, first traces of rupture, release of blend from SGC, progressive deformation leading to change in shape, softening (considering gelatin based SGC) of the dosage unit, etc.

SGC are prone to soften over the duration of the test/experiment while disintegrating and releasing the drug contained within. Therefore, the critical events need to be observed over the QPAT, individually and collectively and need to be noted. Accordingly, the critical events noted below were observed during the disintegration process of artesunate SGC and mapped as a function of time:

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**Table I. Disintegration test/rupture test for soft gelatin capsules described in pharmacopeia.**

<table>
<thead>
<tr>
<th>Test</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2040&gt; Disintegration and dissolution of dietary supplements—rupture test for soft shell capsules (4)</td>
<td>- Medium—water; 500 mL &lt;br&gt;- Apparatus &amp; rpm—USP II &amp; 50 &lt;br&gt;- Time—15 min &lt;br&gt;- The capsule shell is considered ruptured if breached, exposing or allowing the fill contents to escape</td>
</tr>
<tr>
<td>Disintegration test for oral soft capsules (Ph. Eur. Method 2.9.1) (5)</td>
<td>- Medium—water. (When justified and authorized, 0.1 M hydrochloric acid or artificial gastric juice may be used.)&lt;br&gt;- Apparatus—disintegration apparatus.&lt;br&gt;- Time—30 min&lt;br&gt;- All of the dosage units have disintegrated completely.</td>
</tr>
<tr>
<td>Disintegration Test for Suppositories and Pessaries—rectal or vaginal gelatin shell (Ph. Eur. Method 2.9.2) (6)</td>
<td>- Medium—water&lt;br&gt;- Apparatus—specially designed setup&lt;br&gt;- Method—rupture of the gelatin shell of rectal or vaginal capsules occurs allowing release of the contents&lt;br&gt;- Time—30 min&lt;br&gt;- Rupture of the gelatin shell of rectal or vaginal capsules occurs allowing release of the contents</td>
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**Figure 1. A prototype setup to observe the physical events of artesunate soft gelatin capsule.**

![Figure 1: A prototype setup to observe the physical events of artesunate soft gelatin capsule.](image-url)
• A—first sign of physical breakdown of the surface thereby effecting release of the embedded blend of drug product
• B—progressive disintegration of the dosage unit
• C—substantial deformation of the shape of the dosage unit
• D—substantial decrease/change in the size of the dosage unit
• E—near-to-complete disintegration of the dosage unit
• F—physical disintegration of the soft rectal capsule
• G—others relating to the physical structure/character of the dosage unit (soft rectal capsule).

QPAT for artesunate SGC was performed in phosphate buffer (pH 7.2, 1.5% CTAB) on initial and stability samples, whereas only initial samples were evaluated in water. The change in physical nature/appearance at every two-minute interval was recorded as photographs.

Results
The QPAT method was developed using artesunate SGC manufactured during scale-up trials. Because there was no suitable bio-relevant rectal fluid reported in literature, the media recommended for the dissolution testing experiment were phosphate buffer (pH 7.2, 1.5% CTAB) and water. CTAB at a concentration of 1.5% was selected after evaluating several commonly used surfactants in dissolution medium at different concentrations using saturation solubility studies and dissolution trials (these data are yet unpublished and are currently recorded on file). Typically, the complete disintegration of artesunate SGC occurs within 15 minutes. Figures 2a and 2b depict the typical events observed in 10 mL of phosphate buffer (pH 7.2, 1.5% CTAB) and water, respectively, during method development, based on which of the following acceptance criteria was set to assess the quality of the product in routine quality control:

• Not longer than 5 min: first sign of physical breakdown of the surface thereby effecting release of the contained drug/formulation
• Not longer than 10 min: substantial deformation of the shape of SGC
• Not longer than 15 min: near to complete disintegration of SGC.

Accordingly, the data collected on submission batches at initial and stability samples (Figure 3) were assessed against the acceptance criteria. A significantly low co-efficient of variation clearly indicates the reproducibility on observation unit-to-unit. The first event of physical breakdown of the surface occurred (event A) consistently within one minute on initial samples and after the storage of the samples in controlled temperature and humidity of 25 °C/60% relative humidity.
humidity (RH) for 18 months. Similarly, substantial deformation of the shape of SGC (event C) occurred in less than 10 min. However, the third critical event of near-to-complete disintegration (event E) occurred not longer than 20 min., which was higher than the pre-set acceptance criteria of not longer than 15 min. Thus, the acceptance criteria was reset to not longer than 20 min. for the third event (event E) in the final quality specifications.

Discussion

Acceptable disintegration and dissolution in relevant biological fluids is essential for the required performance of the SGC in vivo. With respect to the disintegration test of SGC, various pharmacopeia offer standardized procedures to evaluate the disintegration or rupture of SGC. The United States Pharmacopeia (USP) describes a rupture test for quality control of SGC containing dietary supplements, performed in dissolution apparatus two (paddle) at a rotational speed of 50 rpm with 500 mL of immersion medium (4). British Pharmacopoeia (BP) prescribes a standard disintegration apparatus for SGC not administered by rectal or vaginal route using water as the immersion medium, or 0.1M hydrochloric acid/ artificial gastric juice can be used when justified and authorized. In the case of rectally/vaginally administered SGC, BP uses a different apparatus to contain four to 12 L of immersion medium and a specially designed holder to place the dosage forms. Apparently, these methods do not mimic the biorelevant conditions prevalent in the rectal region, where the volume of liquid is reportedly relatively low (1–3 mL) and the pH neutral at pH 7–8 with low buffer capacity (9). Further, the rectal region is significantly static compared to the other regions of the gastrointestinal tract (10). Hence, development of suitable methods for evaluating the physical attributes of the disintegration of rectally administered SGC in biologically relevant conditions is useful for efficient quality control.

SGCs fail to disintegrate in vitro primarily due to gelatin cross-linking upon aging, when exposed to physical conditions such as high temperature and humidity, ultraviolet radiation, gamma-radiation, rapid drying, and chemical substances such as aldehydes, ketones, imines, and carbodiimides (1). However, gelatin cross-linking does not impact the in-vivo performance of orally administered SGC, because the digestive enzymes (i.e., pepsin or pancreatin) present in the gastrointestinal tract digest the gelatin cross-linking, enabling the disintegration or dissolution of the gelatin shell in vivo. In contrast, the rectal region does not contain digestive enzymes to dissolve cross-linked gelatin, which could lead to product failure. Hence, a biomimetic method to evaluate the disintegration/rupture of rectally administered SGC is even more important to ensure product quality throughout its shelf-life.

The QPAT method developed in this experiment offers a simple, flexible, robust and reproducible way of quality control of rectal SGC. The proposed method can be adopted
even in a setup with limited resources. It also provides opportunity to handle less volume of fluid (<10mL) while maintaining desirable hydrodynamics and visualization of disintegration events. These events can also be video recorded or photographed for robust data maintenance. The opportunity to compare the change in various events during disintegration as a function of time (i.e., during shelf life) in QPAT setup is unique. Though the current scope of QPAT is only for rectal SGC, it can be conveniently applied to other types of SGC, such as vaginal SGC.

The International Council for Harmonization (ICH) guideline Q6A, Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances, provides guidance on the setting and justification of acceptance criteria and the selection of test procedures (11). Accordingly, the decision tree #7.1 in the guidance document allows disintegration testing, instead of dissolution testing, to be used as a performance/quality control test for rapidly dissolving dosage forms (Q>80% in 15 minutes) containing highly soluble drugs (Biopharmaceutic Classification System class I/III), if a relationship between dissolution and disintegration has been established. Similarly, the QPAT method could potentially replace the dissolution testing of rectal SGC containing liquids.

A major shortcoming of the developed method is the difficulty in observing the physical events when the SGC or its contents have intense color. However, this could be overcome by adopting a continuous replacement system using a reciprocating pump or intermittent replacement of whole fluid.

Conclusion
For rectal suppositories, a bio-mimetic disintegration test enables efficient quality control of SGC to assure product quality throughout the shelf-life. In order to simulate conditions within the human body, this method should not replicate requirements for oral gelatin capsules, but must show acceptable disintegration in lower volumes of a medium that is free of digestive enzymes at milder hydrodynamics. QPAT offers a methodology that can be readily adopted for routine quality control. This method offers the advantage of easy setup, even with limited resources. The World Health Organization has already accepted the method for quality control of artesunate SGC for disintegration events (12).

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Data Integrity Topped 2018 Priorities

Agnes Shanley

This year promises to bring more focus on risk management and building a quality culture, says consultant Susan Schniepp.

Although the impact of the US federal government shutdown remains unclear (1), leaders within FDA say they are encouraged by the progress made within the agency and industry during 2018.

According to reports published by the Regulatory Affairs Professionals Society (RAPS) (2), Janet Woodcock, director of FDA’s Center for Drug Evaluation and Research (CDER), singled out generic drugs as a key area where improvement was seen in 2018. She noted an increase in productivity in new molecular entity (NME) development and review at the FDA/Centers for Medicare and Medicaid Services Summit in Washington, D.C. on December 11, according to RAPS.

For 2019, the report said, Woodcock’s top manufacturing and quality-related priorities for CDER include:

- Establishing a framework for overseeing the safety and quality of compounded drugs
- Modernizing the Office of New Drugs
- Implementing new user fee goals and tracking the implementation of serialization legislation.

FDA Commissioner Scott Gottlieb, speaking at the FDLI Enforcement Litigation and Compliance Conference on Dec. 12, 2018, emphasized the importance of risk-based inspection and efforts to ensure that the regulatory burden placed on drug manufacturers is aligned with public health priorities (3). Gottlieb also noted efforts to strengthen FDA’s Office of Regulatory Affairs (ORA) mentioning a program designed to integrate ORA and CDER more closely. He also spoke of global inspection harmonization, singling out the Mutual Reliance Agreement (MRA) with the European Union. An example of MRA in action that he pointed to is the International Active Pharmaceutical Ingredient Inspection Program, which was recently used to share information on valsartan API facility inspections.

For manufacturers and quality specialists, what were the key regulatory achievements in 2018, and what issues promise to dominate this year? Susan Schniepp, executive vice-president of post-approval pharma and distinguished fellow at Regulatory Compliance Associates, shared some insights with Pharmaceutical Technology.

New emphasis on quality culture
PharmTech: What key regulatory trends do you expect to take shape for 2019?
Schniepp: Many of them will focus on quality. The fact that FDA is rethinking its quality metrics program, and that the agency asked for sites to volunteer to be inspected in 2018, was pretty significant. We don’t know what FDA’s final program is going to look like, but we did see signs in its data integrity guidances that FDA would be increasing its attention on how manufacturers approach the task of building a quality culture.

This emphasis will bring FDA more in line with other global agencies, which did not jump on the quality metrics bandwagon but have been more interested in quality culture issues.

Need leading, not lagging, indicators
PharmTech: Were there weaknesses in FDA’s original quality metrics plans?
Schniepp: The agency will continue to tie quality metrics to drug shortages, which will still be an issue in 2019. This approach makes sense, since, once we see metrics, we can do surveillance to identify where problems are developing and how these problems can be deflected, diverted, and remediated before they develop into drug shortages.

However, the metrics that FDA originally selected (e.g., corrective and preventive action [CAPA] turnaround time) were lagging rather than leading...
ones. The industry would benefit more from metrics that indicate when facilities are heading into a problem (e.g., scrap rates, which signal manufacturing problems and tie in closely to the issue of aging facilities).

**Data integrity and compounding issues**

**PharmTech:** Will aging facilities receive more attention from the industry and regulators in 2019?

**Schniepp:** This issue will continue to play out in 2019. At the Parenteral Drug Association (PDA), we’ve spent a lot of time working on post-approval changes, to allow manufacturers to get regulatory relief so that they can modernize facilities more easily. Until this process becomes easier, we will continue to see problems with aging facilities and a rise in scrap rates, reject rates, and aborted lots. These are the metrics that should be tracked.

There are also cost-vs-benefit questions [that tie into drug recalls and commodity drug shortages] and fit right into the aging facilities problem. For example, manufacturers may ask, ‘Why modernize a sodium chloride line when it will not bring any profit?’

**PharmTech:** PDA has been actively involved in a number of regulatory issues and in communicating with FDA. Where has PDA made the greatest progress in this regard in 2018?

**Schniepp:** One important achievement was the development of best practices for laboratory data integrity, and PDA is now working on best practices for manufacturing data integrity, encompassing not only computerized and hybrid, but paper-based systems. It’s so interesting that data integrity keeps coming up as an issue for pharmaceutical manufacturers. Even though the industry went through this in the 1980s with the Barr decision, data integrity continues to rear its head.

**PharmTech:** What are the greatest challenges ahead for building a quality culture within the industry?

**Schniepp:** Investigations into CAPA, things that have gone wrong, and deviations, will continue to be significant problems. Another looming challenge is the fact that, as we move forward with individualized stem and gene therapies, quality risk-based decision making will also have to advance.

These issues will challenge the traditional quality professional. How will one release a lot, for example? And how will investigations into manufacturing problems proceed on site? How is quality going to integrate with manufacturing, so that we get out of our desk chairs and perform lab and site investigations in real time as problems happen, and ensure that the results are meaningful?

**PharmTech:** Do you expect a framework analogous to current good manufacturing practices (cGMPs) to be brought to bear on compounders?

**Schniepp:** It will be interesting to see how FDA manages compounding pharmacies in 2019. Remember, these facilities are essentially making uncontrolled drugs. They don’t have a new drug application (NDA) or filing associated with them, yet a number of large compounding companies are making large lots of product and sending it to hospitals, as permitted by 503b of the Drug Quality and Security Act.

Some of the guidelines that surround traditional aseptic processing are new to them (e.g., they are performing manual manipulations of product under a hood), yet they may not understand why they need to do a media fill or why a particle count is important.

They may also fail to understand how final product testing relates to production and what a certificate of analysis really means. Another question is how should they approach stability? Traditional manufacturers work on container closure issues, but compounders are manipulating closures, and often their product expires within 90 days.

**References**

Currently, a significant proportion of drugs that are approved or in the development pipeline are poorly soluble (1). This proportion may proliferate further as a result of the increasing drive to develop new chemical entities (NCEs) that are molecularly more complex.

Yet, despite offering noteworthy advantages—high selectivity and specificity, for example—more complex molecules also incur their own set of disadvantages. “As drugs become more complex, there is a trend towards higher molecular weight and increased lipophilicity that can decrease aqueous solubility,” confirms Jessica Mueller-Albers, strategic marketing director for oral drug delivery solutions at Evonik.

Julien Meissonnier (vice-president, Science and Technology) and Ronak Savla (scientific affairs manager), both from Catalent Pharma Solutions, agree that increasing molecular complexity impacts a drug’s solubility. “However, solubility is a deceptively complex phenomenon, and its minutiae can lead to different conclusions,” they add. “On the surface, it is simply dissolution of a solute (drug molecule) in a solvent (buffer or media). But, there are dozens of factors that affect solubility.”

Solubility of a substance happens under dynamic equilibrium (2), which means that dissolution and precipitation happen both simultaneously and in an opposing fashion. Therefore, it can be reasoned that intermolecular interactions between the solute (or drug) and solvent must be a consideration along with environmental factors, such as temperature and pressure.

“The factors considered to have the most influence are molecular descriptors such as molecular size, shape, flexibility, and hydrogen-bonding ability,” say Meissonnier and Savla. “A drug’s solubility is also greatly affected by the composition of the solvent system (pH, nature, strength of drug-solvent attractions), which is often underestimated when using aqueous solubility as an indicator for a drug’s solubility in biological conditions.”

Oral ingestion—the importance of permeability
Irrespective of route of administration, pharmaceutical drugs need to be in solution form in order to be absorbed (3), however, considering that the majority of drugs sold in the United States and Europe are administered orally (2) then intestinal permeability is also important. “Solubility, along with permeability, are the two most important factors affecting oral drug absorption and underlying the Biopharmaceutics Classification System (BCS) and Developability Classification System (DCS),” say Meissonnier and Savla.

BCS and DCS are classification systems used to predict what will impact the in-vivo performance of drugs (4,5). Predictions performed with these systems are restricted using solubility and permeability as parameters (2). Drugs are considered to be highly soluble when the highest-dose strength is soluble in 250 mL (or less) of aqueous solution (according to the BCS) or when the highest total dose in 500 mL (or less) of aqueous buffer pH 6.5 (according to the DCS).

However, for pharmaceuticals, the solvent of choice is water, in which most drugs are poorly soluble (2). Solubility, being the most important rate-limiting parameter for orally administered drugs, is a major challenge for the formulation scientist. “The increasing numbers of poorly soluble NCEs increase the importance of bioavailability enhancing technologies to enable development success,” add Meissonnier and Savla.

Overcoming solubility challenges
Solubility improvements can be achieved through several means, which fall under two main categories. “The two main methods to alter the solubility or dissolution of a drug substance are through either material engineering or formulation development,” says Mueller-Albers.
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“A mix of competencies that can be tailored to the specific needs of a project, including particle engineering, milling, solid dispersions, silica technologies, and formulations that enable rapid disintegration can be leveraged to enhance the solubility and bioavailability of drugs.”

An initial step in tackling solubility challenges for Meissonnier and Savla is optimization of the drug molecule itself through chemical design, followed by evaluation of the physical form of the molecule and its impact on solubility. “Despite these efforts, a growing number of molecules reach the preclinical and clinical development stage with persisting solubility issues, requiring advanced formulation technologies,” they add. “Several formulation technologies are designed to resolve solubility issues.”

However, they note that only a few of these formulation technologies demonstrate all the criteria desirable in drug development that can be used throughout clinical development and commercialization.

Formulation considerations
“First and foremost, formulating a poorly soluble molecule requires an in-depth characterization of its underlying bioavailability challenge,” stress Meissonnier and Savla. “Way too often, formulation scientists jump on the solubility challenge and try to resolve a partially defined or wrongly defined problem.”

For example, they explain, if trying to improve solubility of a formulation when the issue actually lies with dissolution rate, chemical instability, and/or high first-pass metabolism, time and effort could be wasted on the wrong development pathway. “The most important consideration revolves around employing the right models to characterize the molecule’s developability problems,” they continue. “It is key to leverage and develop the right physiologically based pharmacokinetic (PBPK) models to evaluate if the absorption hurdle is only solubility based. According to the Biopharmaceutical Drug Disposition and Classification System (BDDCDS), most poorly soluble and highly permeable drugs are subject to liver metabolism, and in several instances, drug metabolism at the gut wall and in the liver may be the main hurdles.”

Using the DCS, formulators can determine whether dissolution kinetics (DCS IIa) or intrinsic solubility (DCS IIb) is the main hurdle. If solubility is the main hurdle to formulation success, then leveraging the right model to bridge drug substance properties with formulation technology becomes critical, according to Meissonnier and Savla. “One of the most important features of the DCS model is factoring in the total dose in relation to solubility,” they say. “In the very first animal studies, drugs are often tested at 10s–100s of milligrams per kilogram of body weight, which magnifies the solubility hurdle and may suggest the selection of the most complex technologies, whereas more simple solutions would be required for human clinical studies.”

There are numerous solubility enhancing technologies available, and for companies developing innovative drugs, selecting the best technology can be a difficult process. “Among many technologies, only a few have made it successfully to the clinic, and on to market. For DCS IIa molecules, particle size reduction (micronization and co-micronization) can overcome the slow dissolution rate, and for DCS IIb molecules, only lipid-based formulations and amorphous dispersions (made via spray drying and hot melt extrusion) have demonstrated commercial success,” explain Meissonnier and Savla. “Therefore, parallel screening of those technologies to select the most appropriate to the development stage is key.”

Mueller-Albers also notes the importance of a parallel approach. “It’s recommended to use predictive tools that can minimize development costs, as well as process technologies and equipment that avoid interactions with the API, enable higher drug loadings, and improve stability,” she says. “Finally, it’s always important to review the physical properties of the drug, ease-of-manufacturing, and the patent position.”

Dissolution testing
“A fundamental goal of pharmaceutical development is to optimize drug levels available in the body to match the therapeutic window, so that the desired therapeutic effect is achieved without adverse side effects,” Mueller-Albers states. “The effectiveness of any oral dosage form depends upon the intrinsic ability of the drug to reliably dissolve in the fluids of the gastrointestinal tract prior to it being absorbed into the blood stream. The rate of dissolution is a critical factor in this process.”

An important tool used within the pharma industry to determine the performance of oral solid dosage forms is that of dissolution testing (6). “Dissolution testing is a standardized method for measuring the rate of drug release from a given dosage form to optimize the formulation,” adds Mueller-Albers. “Tests must not only be robust and reproducible, but be able to detect any key changes in product performance between different formulations or batches. It is also essential that in-vitro dissolution matches in-vivo conditions. If the dissolution procedure is well designed, it should help to accelerate drug development by an effective selection of prototype formulations and de-risk the clinical studies, which are necessary in the drug product approval process.”

Meissonnier and Savla say that the first step should be to establish whether the dissolution testing is intended to be used to predict in-vivo performance or for quality assurance/control (QA/QC). “There are guidance documents and guidelines published by regulatory authorities and scientific organizations that deal with scale-up and post-approval changes, bioequivalence, and biowaivers,” Meissonnier and Savla continue. “A design-of-experiments (DoE) approach should be applied to develop a control strategy and define a design space. The API solubility and stability in the dissolution media should be part of the test set-up. Part of the dissolution test validation should assure that other components (i.e., excipients) do not interfere with ultraviolet absorbance, and that the calibration curve is linear and covers the lowest to highest concentration achieved during testing.”

When specifically looking at development projects involving poorly soluble drugs, Mueller-Albers explains that bio-relevant media, such as fasted (FaSSIF)
or fed-state simulated intestinal fluid (FeSSIF), can be employed. “These media contain solubilizing ingredients such as bile salts and phospholipids at physiological concentrations that are more precise in simulating the in-vivo solubility and dissolution rate of poorly soluble compounds than pure buffer media,” she says. “Dissolution volumes used in the in-vitro test can also be adapted to better reflect the physiological situation. Dissolution testing for QC purposes may also require a non-physiological pH, or the addition of solubilizers, such as sodium lauryl sulfate, to enable different product qualities to be differentiated based on the dissolution behavior.”

Conclusion
“Poor solubility was once considered to be a ‘show-stopper’ in formulation development,” summarizes Mueller-Albers. “However, while the risk of solubility has been reduced, there are still many drug candidates with physical characteristics that are incompatible with conventional processing technologies. Despite many pharmaceutical companies establishing standard processes for the development and manufacturing of drug products with poor solubility, in my opinion, there is still a strong need to select development partners that can provide rapid, reliable support into clinical studies.”

Considering oncology, Meissonnier and Savla state that this trend of compounds reaching patients with unaddressed solubility issues is magnified as clinical development pathways are often accelerated, leading to the first formulation that is investigated making it through to market launch. “So, poorly soluble oncology molecules (e.g., most protein kinase inhibitors) can reach the market with sub-optimal formulations and persistent solubility shortcomings,” they note.

If these solubility issues are not addressed, there may be dire consequences. “Solubility issues may result in higher pharmacokinetic variability (intra- and inter-patient) and a positive food effect (sometimes translated into a marked increase in serum concentrations of tenfold or higher). These detrimental properties, often combined with a narrow therapeutic index, can lead to significant challenges in patients and avoidable black box warnings,” Meissonnier and Savla warn. “Therefore, the early adoption of the right formulation technology to address poor solubility can deliver significant patient benefits and complement market differentiation.”

References
Active and intelligent packaging technologies benefit brand owners, caregivers, and patients.

Smarter Packaging Comes to the Pharma Market

Hallie Forcinio

Active and intelligent packaging technologies benefit brand owners, caregivers, and patients.

S
mart packaging offers benefits to each stakeholder in the pharmaceutical supply chain. It can enhance patient compliance/adherence; confirm authenticity; support tracking, anti-counterfeiting, and addiction prevention efforts; protect shelf life; and bolster sustainability profiles.

Divided into two segments, active packaging and intelligent packaging, global demand for smart packaging is forecast to grow at a compound annual growth rate of 8% to reach a projected value of $7.8 billion by 2021 (1). Active packaging enhances functionality and includes technology such as scavengers, desiccants, and color-changing inks. Intelligent packaging is more interactive and provides a way to receive, store, and deliver information. Associated technologies include QR codes, near-field communication (NFC) and radio frequency identification (RFID), printed electronics, smartphones, smartphone apps, the Cloud, and the Internet.

“Technological progress is providing new possibilities for drug packaging,” says Benjamin Rist, product manager at August Faller Group. “The Smart Packaging Solutions show how drug packaging will improve patient compliance and facilitate the handling of drugs in the future.”

Active packaging

Color-changing BlindSpotz Tamper Heat and Tamper Freeze inks from Chromatic Technologies enable the detection of product tampering by heat and sub-zero temperature exposure. Before the development of the Tamper Freeze inks, most tamper indicators only revealed heat tampering. Lyle Small, the founder of Chromatic Technologies, explains, “Criminals have figured out that the way to get around high-heat tampering indicators is to ‘go cold’ by exposing packaging to very low temperatures. This can ‘delaminate’ many adhesives without activating a tamper-heat indicator. The BlindSpotz Tamper Heat and Tamper Freeze inks eliminate both threats” (2).

Printable on seals, tape, labels, and packaging substrates, the technology activates within a 5 °C window and can be printed with adhesives and overprint varnishes. The Tamper Freeze ink turns from clear to blue when exposed to temperatures below -10 °C, while Tamper Heat ink turns from gray to orange (or gray to pink) if exposed to heat greater than 65 °C (see Figure 1). In addition, Tamper Heat ink maintains color if exposed to high temperatures (greater than 100 °C) and lasts much longer on the shelf than existing “heat-irreversible” systems (2).

The temperature-sensitive messages are easily incorporated into existing graphics. “If the stakeholder seeks an overt message, it will be easy for everyone in the supply chain to recognize if tampering has taken place. But if an investigation is underway, covert symbols can appear (to confirm tampering) without alerting the bad actors that they’ve been detected,” says Patrick Edson, chief marketing officer at Chromatic Technologies.

The BlindSpotz line also includes printable freeze alert technology so caregivers and consumers can verify a cold-sensitive drug has not been exposed to freezing and is viable for injection. If the product has experienced freezing conditions, the ink reveals a “Frozen. Do Not Use.” message or a frown-face icon. The technology offers an inexpensive way to monitor the flow of drugs such as cholera, influenza, and HPV vaccines being shipped internationally. “All these vaccines need an easy alert tool to indicate if, at the time of injection, they have been damaged by temperature or tampering,” says Edson.
He continues, “Current sensor technology for drugs and pharma requires a separate label or device to be used and can cost $1–$5 each, and then there is the additional cost of application. [Printable technology provides] highly accurate, affordable, and scalable solutions that can be implemented for pennies.”

**Intelligent packaging**

“This is the era of smart-everything,” reports Steve Tallant, director of Product Management and Marketing at Systech. He continues, “It is an expectation and not an option to distribute connected products. And connected does not mean just a printed link to a website. True, two-way communication is an ever-increasing reality and norm. Pharmaceutical packages need to be authentic, safe, and now connected.”

As a result, intelligent packaging technology is being incorporated into caps, labels, folding cartons, and flexible packaging materials. These formats offer high potential “for patient compliance, safety, and therapeutic success,” notes Rist.

For example, Kisico’s NFCap, equipped with an NFC chip, works with a smartphone app and provides covert product protection. Functions include product authentication, recording of when and where the bottle was opened, presentation of dosage instructions and product information, and dosage and expiration date reminders.

Closure Systems International (CSI) has introduced a range of NFC chip-equipped caps through a partnership with Talkin’ Things (see Figure 2) (3). Instructions in words or pictures on the package label or shrink sleeve direct consumers to use their phone to initiate the interaction.

One-stage tags support direct-to-consumer communication, while a two-stage tag adds an anticonte channeling function. David McCall, Business Development, Diversified Markets at CSI, explains, “CSI’s two-stage Talkin’ Cap provides brands with an extra level of protection and traceability to fight against global counterfeiting. Every day, pharmaceutical companies fight consumer health risks and company financial risks associated with the counterfeiting of their products. Our goal is to work with companies to implement a technology that will minimize and mitigate that very real and costly threat of global counterfeiting.”

A partnership between Multi-Color Corp. and Talkin’ Things melds NFC technology with pressure-sensitive, shrink-sleeve, or roll-fed labels. Digitalizing products via NFC labels enables the real-time management of promotions and personalized mobile promotions and provides a way to reward customers directly through the product and increase brand loyalty. Talkin’ Things also can provide Multi-Color with intelligent packaging technology based on RFID, augmented reality, Internet of Things sensors, or electronic article surveillance (anti-theft) protection (4).

**Intelligent packaging provides a way to receive, store, and deliver information.**

Schreiner MediPharm introduced an NFC-equipped label for autoinjectors in October 2018 at the PDA Universe of Pre-filled Syringes and Injection Devices in Orlando, FL. Easily adapted to existing label designs, the Autoinjector-Label wraps around the unit, including the cap, and can be read via a smartphone app. Before opening the cap for the first time, the patient can confirm the product is in its original sealed condition. The NFC technology also allows pharmaceutical manufacturers to present interactive product information, demo videos, or special apps to help patients through the self-medication process. Integrated geo-tracking makes it possible to detect gray market activities. The digital Autoinjector-Label adapts to existing label designs and does not affect the normal operation of the device (5).

One criticism of NFC and RFID tags is the presence of non-recyclable materials. Stora Enso eliminates that objection with its ECO sustainable RFID tag technology. The paper-based RFID tag eliminates plastic and is recyclable along with the paper label (6).
With e-Fingerprint technology from Systech, any printed barcode can serve as a unique identifier. The winner in the Excellence in Pharma: Supply Chain, Logistics, and Distribution Category at the CPhI Pharma Awards in October 2018, the e-Fingerprint technology relies on microscopic variations in substrate and print and a smartphone app (7). "Systech’s e-Fingerprinting solution changes everything about smart packaging without changing anything at all," states Tallant. He explains, "Due to the inherent characteristics of the printing process, there are micro-differentiations in printed output." As a result, the digital e-Fingerprint is completely covert and non-replicable by counterfeiters. The technology relies on Systech’s vision capabilities to look microscopically, at line speed, at the printed output and derive a unique e-Fingerprint for each package. "Then, using a smartphone app, a user is able to authenticate the item [from] anywhere in the world. Because the item is uniquely identified, additional information ... like expiry, lot, batch, ingredients, and recall notices can be presented interactively with a user," says Tallant.

He reports, “We have pharmaceutical companies deploying our e-Fingerprint solution globally to fight not just counterfeiting, but diversion of product out of the legitimate supply chain. Because of vastly different price points for medicines globally, it can be very lucrative to divert medicines out of low/no-cost geographies and send them for great profits into high-price geographies. [When products are e-Fingerprinted, manufacturers can] inspect product globally and identify diverted product immediately ... and stop the practice. This helps keep medicines in the countries that need them desperately.”

Patients and drug makers benefit from trusted authenticity and safety globally. Drug makers gain significant supply-chain protection from diversion and counterfeiting.

Smart Packaging prototypes from August Faller Group showcase other potential benefits. “With our Smart Packaging solutions, we have developed three prototypes that take into account the advancing digitalization in the e-health market and the growing interest in interactive packaging solutions,” says Rist. The Counting Device folding carton is equipped with a small e-paper display and electronic controls (buttons) to improve compliance (see Figure 3). In use, the patient confirms he/she has taken the tablet by pressing a button on the front of the folding carton. If the supply of tablets starts to get low, the e-paper display shows a warning and reminder to refill the prescription. A tiny microcontroller (storage medium-on-chip) is powered via a battery integrated in the packaging. The flat structure of the electronics was a central requirement for easy integration in a pharmaceutical package and was accomplished via a printed circuit board mounted on the back of the carton and an e-paper display on the front (8).

The Counting Device is one of three Smart Packaging prototypes developed by Faller in conjunction with MSC Technologies and Pforzheim College. The other two designs include a Level Indicator carton also equipped with a Level Indicator carton and an e-paper display on the front (8). Flat electronics with an economical microcontroller, tiny battery, and adhesive e-paper display integrate into the medication packaging without significantly increasing the size of the box (8).

For flexible packaging and labels, the SecuriLam laminate from TruTag Technologies offers both authentication and traceability functionality. Microscopic, encoded silica particles, or TruTags, are pre-embedded into standard adhesive laminate film. The food-grade silica particles are invisible to the naked eye, do not affect the finish of the laminate or final product, and are readable via proprietary authentication devices. Programmability allows brand owners to segment their packaging. Programmed information can include manufacturing location, product type, or authorized geography to authenticate product and identify diversion (9).

References
HPAPI Best Practices: Development, Manufacturing, and Particle Engineering

ON-DEMAND WEBCAST  Aired December 13, 2018

Register for this free webcast at www.pharmtech.com/pt_p/hpapi

Event Overview
Improved candidate compound screening and more targeted drug action are bringing more highly potent active pharmaceutical ingredients (HPAPIs) to the drug development pipeline. Many of these compounds require particle engineering to meet target product profiles. HPAPIs and their intermediates require specialized handling capabilities and expertise for safe development, scale-up, and manufacturing. In this webinar, learn about best practices and review representative case studies for HPAPIs across the development cycle.

Key Learning Objectives
- Key criteria for containment in development and manufacturing highly potent/extremely potent compounds
- Glove-box design optimization and procedures for particle-size reduction of HPAPIs
- Effective approaches for accelerated scale-up and technology transfer

Who Should Attend
- Large pharma, mid-size pharma, biotech companies
- Technical positions involved in process development and scale-up — early to late development or commercialization — of highly potent compounds
- Scientists, Engineers, R&D Managers, Senior Managers

Presenters
- Maurits Janssen, PhD
  Senior Director,
  Head of Commercial Development
  Lonza Pharma & Biotech
- Milko Leone, Eng
  Head of Engineering Department
  Lonza Monteggio

Moderator
- Rita Peters
  Editorial Director
  Pharmaceutical Technology

For questions contact Kristen Moore at kristen.moore@ubm.com

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Pharmaceutical Technology
Outsourcing of manufacturing activities is expected to increase in 2019.

Essentially all biopharmaceutical industry-related indicators and trends are supporting continued incremental increases in outsourcing of pre- and commercial API and biopharmaceutical product-manufacturing services to contract manufacturing organizations (CMOs). This is positive news for CMOs. BioPlan Associates’ survey of bioprocessing professionals overall confirms that outsourcing to CMOs is being viewed increasingly as a desirable option, with expectations for more outsourcing in the future (1).

CMOs are already a core component of the biopharmaceutical industry, and their use and importance will further incrementally increase over time. Routine services and products with smaller markets will be outsourced more frequently, and products requiring novel bioprocessing, where expertise or capacity remain limited, will also be outsourced more frequently, such as cellular and gene therapies. Most innovator drug companies continue to retain manufacturing and development of their prospective blockbusters in-house.

The financial outlook for CMOs is solid.

The financial outlook for CMOs is solid, with growth in revenue tracking that of the overall biopharmaceutical sector, which consistently grows at more than 12% annually. CMOs continue to expand capacity, staff, etc., to try to retain clients as their products advance in development. Total annual biopharmaceutical CMO revenue was approximately $3.4 billion in 2018 and is expected to grow to about $3.8 billion in 2019. Biopharmaceutical CMOs remain a relatively small niche, however, with chemical substance-based drug outsourcing revenue more than 10 times that of the biopharmaceutical sector.

Despite being just a small part of the overall biopharmaceutical industry, CMOs play important roles. CMOs currently commercially manufacture approximately 30% of marketed mainstream (recombinant) commercial products, although this remains concentrated among a few, large-capacity CMOs. Most CMOs primarily support R&D and early-phase support—and only a minority performing commercial manufacturing—so, in general, CMOs’ involvement in earlier-phase aspects of product development and manufacturing is even larger than with commercial manufacturing. CMOs also play an important role in new bioprocessing technology development and adoption, with CMOs often the first (compared with developer companies) to implement new technologies. CMOs often have much more technical expertise than developer companies, including with new technologies, with CMOs having worked on more products/projects and using a wider variety of technologies.

A decade or more ago, Big Pharma and other well-established developer companies outsourced as much work as possible to CMOs, often without critical analysis. Most biopharmaceutical companies traditionally turned to outsourcing to control costs and/or manage their internal staff and resources. Biopharma companies are now increasingly taking a more strategic view of outsourcing and seeking to outsource as much as possible. Most companies periodically re-evaluate their core competencies and rationally decide how they will manage their R&D, manufacturing, and related outsourcing. As a result, almost every area of R&D and manufacturing is considered a candidate for outsourcing (1).

The number of products in development continues to grow, with this carrying over to CMO outsourcing. FDA approved approximately 25 new biopharmaceuticals in 2018 (1), and the number of annual approvals is
Outsourcing Outlook

expected to increase in coming years, as new classes of products receive approvals, particularly biosimilars and cellular and gene therapies. In the next five years, the number of approved biosimilars will exceed the number of approved mainstream products.

The evolving mix of biopharmaceuticals in the development pipeline is expected to increase outsourcing to CMOs.

The evolving mix of biopharmaceuticals in the development pipeline is also expected to increase outsourcing to CMOs, because CMOs often have more capabilities and expertise in new areas of bioprocessing than developer companies. Product types, classes, and the underlying molecular structures of products in R&D continue to diversify.

Rather than just familiar-type recombinant proteins and monoclonal antibodies, CMOs are often the pioneers in terms of manufacturing novel products, including antibodies with novel core structures/backbones, antibody–drug conjugates (ADCs), cellular therapies, gene therapies, RNAi, pegylated proteins, and other novel types of products. Also, lesser innovative classes of products are often outsourced; CMOs report a 15% increase in business in recent years from biosimilars projects.

Essentially, every successful CMO is continually expanding its capacity and staff/expertise. The industry is starting to see a major trend for CMOs adding 1000–2000-L single-use bioreactor process lines for commercial manufacturing as products currently in development manufactured with single-use systems advance to approvals.

In the past year, BioPlan has identified approximately 180,000 L of single-use systems with capacities greater than 1000 L added as CMO expansions or new facilities (2). As CMOs develop this 'entry-level' commercial scale single-use capacity, the number and percentage of marketed products commercially manufactured by CMOs will further increase, at the expense of stainless steel-based bioprocessing.

Figure 1: Biopharmaceutical manufacturing facilities outsourcing no production 2006–2018.

(% Organizations Manufacturing 100% In-house)

(No Outsourced Manufacturing, 2006-2018)

<table>
<thead>
<tr>
<th>Year</th>
<th>Mammalian Cell Culture</th>
<th>Microbial Fermentation</th>
<th>Cell or Gene Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018</td>
<td>30.0%</td>
<td>34.1%</td>
<td>30.0%</td>
</tr>
<tr>
<td>2017</td>
<td>44.2%</td>
<td>43.8%</td>
<td>47.1%</td>
</tr>
<tr>
<td>2016</td>
<td>50.0%</td>
<td>50.0%</td>
<td>46.2%</td>
</tr>
<tr>
<td>2015</td>
<td>44.6%</td>
<td>45.2%</td>
<td>47.6%</td>
</tr>
<tr>
<td>2014</td>
<td>57.0%</td>
<td>57.6%</td>
<td>57.6%</td>
</tr>
<tr>
<td>2013</td>
<td>52.4%</td>
<td>47.1%</td>
<td>52.4%</td>
</tr>
<tr>
<td>2012</td>
<td>44.2%</td>
<td>47.1%</td>
<td>44.2%</td>
</tr>
<tr>
<td>2011</td>
<td>67.6%</td>
<td>67.6%</td>
<td>67.6%</td>
</tr>
<tr>
<td>2010</td>
<td>57.6%</td>
<td>57.6%</td>
<td>57.6%</td>
</tr>
<tr>
<td>2009</td>
<td>52.4%</td>
<td>52.4%</td>
<td>52.4%</td>
</tr>
<tr>
<td>2008</td>
<td>45.2%</td>
<td>45.2%</td>
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<tr>
<td>2007</td>
<td>57.6%</td>
<td>57.6%</td>
<td>57.6%</td>
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<tr>
<td>2006</td>
<td>64.2%</td>
<td>64.2%</td>
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Outsourcing Outlook

Survey data and trends
Developers generally outsource a higher percentage of projects/products involving mammalian vs. microbial expression systems. The historical picture of respondents to the annual BioPlan survey reporting that they do not outsource bioproduction is shown in Figure 1.

Biopharma companies are now increasingly taking a more strategic view of outsourcing and seeking to outsource as much as possible.

In 2018, 30% of survey respondents reported no mammalian outsourcing, meaning that 70% outsourced at least some of their mammalian projects/products; 43% reported no (57% reported some) outsourcing of microbial work. The percent not outsourcing of any mammalian or microbial work has generally decreased (i.e., percent reporting some outsourcing has increased) since 2006. Comparable small portions, approximately 15%, report outsourcing the majority of their mammalian and microbial work. Growth and trends in outsourcing of microbial work remain somewhat unclear, with the largest CMO market, the United States, relatively lacking in microbial CMOs and GMP capacity greater than 100–200 L; Europe is the clear leader in microbial CMOs and GMP capacity.

When developer respondents to the 2018 survey were asked about expectations for outsourcing any work (any expression system) in five years, 72.3% projected at least some mammalian and 58.3% said they expected to outsource at least some microbial work. More than 61% of respondents are currently outsourcing at least some API manufacturing.

But this percentage was lower than for many tasks outsourced to contract research organizations (CROs), including 77.8% outsourcing some analytical testing/bioassays, and 72.6% outsourcing at least some toxicology testing. More than one-quarter of the respondents (27.7%) cited expectations/plans to outsource more biopharmaceutical API manufacturing in the next two years, increasing from 12.4% in 2010.

The US continues to be the destination for the largest portion of outsourcing to foreign CMOs, with 30.1% of respondents citing US facilities as likely being considered for CMO work within five years. Figure 2 shows the top 10 countries, other than their own, survey respondents said they expected to be a destination for outsourcing of their international expansions in the next five years. Among US respondents, China was the top destination, cited by more than 50%.

Despite these industry expectations of more outsourcing to China, CMOs are not fully permitted in China; just a few select companies currently participate in government-run CMO pilot programs. Once China turns on its domestic bioprocessing industry, China may become a major offshoring destination, even if these CMOs are hired to only manufacture products for China’s massive domestic market.

BioPlan expects Chinese CMOs to capture business, potentially doing this at the expense of Indian CMOs. India appears to be focusing on serving its own and international markets for lesser-regulated biogenerics, while, according to BioPlan studies, nearly 85% of the Chinese biopharmaceutical industry targets GMP manufacture for their own domestic and Western markets.

References
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Catalent Invests $200 Million in Wisconsin and Indiana Sites

Catalent announced on Jan. 7, 2019 a $200-million investment in its biologics business to expand drug-substance manufacturing capacity and drug-product fill/finish capacity. The investments, phased over a three-year program, will be carried out at the company’s biologics manufacturing sites in Madison, WI, and Bloomington, IN. This follows a December 2018 announcement the company was investing $14 million in packaging capabilities at the Bloomington site.

Mammalian cell-culture capacity will be increased at Madison with the build-out of two new suites, each with a 2 x 2000-liter single-use bioreactor system, providing additional clinical and commercial production capacity at the 2000- or 4000-liter batch scale as well new laboratories. Work is expected to be completed by mid-2021 and will more than double Catalent’s commercial biomanufacturing capacity, the company reports.

Additionally, fill/finish capacity at the Bloomington site will be expanded by 79,000 ft², with both GMP and non-GMP capabilities. A high-speed flexible vial line, using both ready-to-use components and bulk filling at a filling speed of 300 units per minute, will be installed along with a high-speed flexible syringe/cartridge line with a filling speed of more than 300 units per minute, and a fully automated vial inspection machine.

AbSci, Sanofi in Manufacturing Partnership

On Jan. 9, 2019, AbSci, a biotherapeutic discovery and manufacturing technology company, announced a manufacturing collaboration with Sanofi to improve two of Sanofi’s biotherapeutics. Under the terms of the agreement, AbSci will apply its Escherichia coli (E. coli) manufacturing platform, SoluPro, and its optimization assay system, to two of Sanofi’s biotherapeutic molecules. AbSci reports that its technology platform can rapidly achieve optimized, scalable, high-quality, high-titer production of any class of biotherapeutic molecule, including traditionally difficult-to-manufacture molecules and next-generation scaffolds. The collaboration will take place at AbSci, located in Vancouver, WA, and funded by Sanofi.

During development, SoluPro can reportedly produce gram quantities of material for preliminary screenings in a matter of days instead of weeks. AbSci states that the platform has a demonstrated track record expressing difficult proteins and achieves higher protein production levels than mammalian systems, which allows scientists to access previously elusive and untestable therapeutic proteins. Once therapeutic candidates have been identified, the platform scales seamlessly for commercial production, therefore eliminating the six-to-12-month cell-line development process. By returning biomanufacturing to its E. coli roots, AbSci says it aims to replace Chinese hamster ovary cell and other mammalian expression platforms as the preferred expression host.

Rentschler Biopharma Completes Acquisition of US Manufacturing Site

Rentschler Biopharma, a contract development and manufacturing organization (CDMO) for biopharmaceuticals, completed the acquisition of a manufacturing facility from an affiliate of Shire, the company announced in a January 3, 2019 press release.

The 93,000-ft² site with approximately 70 employees is located near Boston in Milford, MA, and it is the German company’s first manufacturing facility in the United States. Under the terms of the agreement, Rentschler Biopharma will continue to manufacture for Shire at the site.

Fujifilm Invests in Biopharmaceutical Production Capacity

Fujifilm plans to invest approximately JPY 10 billion (approximately US$90 million) to expand its biopharmaceutical CDMO business, FUJIFILM Diosynth Biotechnologies (FDB), the company announced on Jan. 7, 2019.

This investment will include the expansion of existing production facilities at its North Carolina location. Further investments are planned at the company’s other locations.

Investments will include the addition of 2000-L single-use cell-culture manufacturing trains, cell-culture purification suites, and new microbial recovery suites to its existing facilities in North Carolina. These additions will increase cell-culture manufacturing capacity by approximately 25% and microbial capacity by approximately 50% at its North Carolina location. The company expects that the increased production capacity will be ready for cGMP manufacture by early 2020. Fujifilm has committed to grow its CDMO business to meet a JPY 100 billion sales target by March 2024.

Cambrex Acquires Avista Pharma

On Jan. 3, 2019, Cambrex, a provider of generic APIs, small molecule, and finished dosage form products and services, announced that it completed the $252-million acquisition of Avista Pharma Solutions, a contract development, manufacturing, and testing organization, from Ampersand Capital Partners. Cambrex reports that the transaction, announced in November 2018, strengthens Cambrex’s position as a small-molecule CDMO across the entire drug lifecycle. Avista’s four sites in Durham, NC; Longmont, CO; Agawam, MA; and Edinburgh, Scotland, UK will be integrated into Cambrex’s global network, as well as the company’s service offerings ranging from API and drug product development and cGMP manufacturing to stand-alone analytical, microbiology testing, and solid-state sciences.
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Understanding the differences in inspection processes is the key to successful global expansion, according to Siegfried Schmitt, PhD, vice-president Technical, PAREXEL Consulting.

Q. We are a medium-sized company in Europe, specializing in gene-therapy products. So far, we have only marketed our products in Europe, but we are planning a global expansion. By now, we are familiar with the European inspectors and how they inspect. How can we prepare for inspections from overseas agencies? We hear that there is no harmonization in expectations?

A. Congratulations on your plans and being proactive in preparing for these inspections. To some degree, inspectorates from around the world are making attempts at harmonizing how they inspect. Regulatory agencies that belong to Pharmaceutical Inspection Co-operation Scheme (PIC/S) follow a harmonized inspection process. It is sensible to familiarize oneself with these procedures, which are freely available on the PIC/S website (1).

Other drivers for harmonization are mutual recognition agreements (MRAs), which require agencies to recognize each other’s competence and equivalence. Currently, the United States and the European Union (EU) are in the process of finalizing such an MRA (2). As you will already be aware, inspectorates of the EU’s member states, the National Competent Authorities, are all peers (i.e., recognizing each other’s inspections as completely equivalent) (3).

That said, you may still encounter differences in inspection process and style, and moreover, differences in opinion from your inspectors. Why might this be? There are three main contributions:

- The law: different national regulations
- The approach: country-specific inspection processes and requirements
- The human factor: personal preferences of the inspectors.

To make your inspections as smooth and successful as possible, you need to acquaint yourself with all three aspects and prepare for them. A pharmaceutical firm is legally required to comply with the national regulations in any country it wishes to market its products. Therefore, you must be familiar with the regulations. For example, your products will have to comply not merely with the pharmacopeia in your native country, but also with those of the country the overseas inspector is from. Do not be surprised if an inspector wants to see that you do possess a copy of that document and that you can read it if it isn’t in your native language.

Many agencies publish details on how they inspect and often also provide additional information on the inspection process and the agency’s expectations. The United Kingdom’s Medicines and Healthcare products Regulatory Agency (MHRA), for example, has a blog (4). FDA publishes guidance for industry documents (5), and Australia’s Therapeutic Goods Administration updates information on their inspection approaches regularly on their website (6). It is essential to stay informed on the inspection process, as some agencies may have specific requirements. Russia’s Roszdravnadzor, for example, requires you to provide certified third-party translators with good manufacturing practice expertise for its inspection; or Colombia’s National Food and Drug Surveillance Institute (INVIMA) expects you to have all observations resolved by end of inspection. Here, the difficult part is that not all the expectations are included in the guidance documents. The best way to get access to such detailed information is to use the help of professional service providers and to interact with peers (e.g., at conferences or through industry associations).

The last point, namely an inspector’s personal opinions, is one you simply have to address at the time of the inspection. As with all inspections, courtesy and professionalism will go a long way.

To answer your question: be prepared by having a sound understanding of the regulations and the regulatory inspection processes, including the unwritten expectations. Regulatory intelligence is essential as regulations change continuously and so do the inspection processes.

References
4. MHRA, MHRA Inspectorate Blog, mhrainspectorate.blog.gov.uk.
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