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HPAPI Capacity Challenges

Susan Haigney

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Does the pharmaceutical industry have adequate access to contained equipment, facilities, and infrastructure for the manufacture of highly potent APIs?

The pharmaceutical industry has been experiencing an increase in demand for drug products that contain highly potent APIs (HPAPIs), both in the United States and in Europe. According to Adam Bradbury, associate analyst at PharmSource, a GlobalData product, the number of innovative pharma product approvals requiring containment has been increasing since 2008 (see **Figure 1**). A majority of these products have been in the oncology and pain treatment areas. "The most commonly approved US product types requiring containment were (highest to lowest) controlled drugs, cytotoxics, steroids, immunosuppressants, kinase inhibitors, and nucleotides, which is indicative that many of these treatments are for oncology or pain relief," says Bradbury.

Maurits Janssen, head of Commercial Development, API Development & Manufacturing, Lonza Pharma & Biotech, agrees. "We are witnessing a rise in the importance of drugs that include one or more HPAPI component. These molecules are useful in treating cancer, diabetes, autoimmune diseases, and other indications, and pharma and biotech companies are taking notice and incorporating them into innovative therapies."

GlobalData's Drugs by Manufacturer database reports that 532 novel approved drugs approved in the US and the EU require containment. "There is a tendency for both high potency drugs' API and dose manufacture to be outsourced rather than manufactured in-house, although some of these products will also be dual sourced (both manufactured in-house and outsourced)," says Bradbury.

GlobalData's research supports that statement; API manufacturing is outsourced for 255 of those drugs; 317 drug products are produced by contract manufacturers. In-house production is used for 201 highly potent drug substances and 295 HPAPI-based drug products.

Approximately 60% of HPAPIs in development are for oncology drugs (see **Figure 2**), which, according to Bradbury, points to an increase in demand for HPAPI manufacturing capacity. Because HPAPIs have special requirements for handling and containment, those companies looking to outsource HPAPI production may encounter challenges locating a contract development and manufacturing orga-

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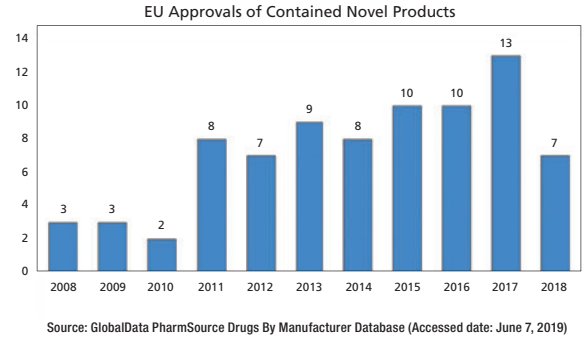
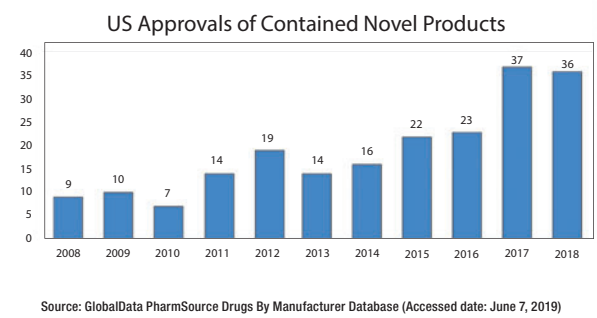
Figure 1: Number of innovative pharma product approvals in the European Union and United States from 2008–2018.



Source: GlobalData PharmSource Drugs By Manufacturer Database (Accessed date: June 7, 2019)



Source: GlobalData PharmSource Drugs By Manufacturer Database (Accessed date: June 7, 2019)

nization (CDMO) to develop and manufacture these hazardous materials.

Projecting capacity supply and demand

"There is sufficient capacity in the market but obtaining additional capacity to boost business growth via acquisition is not economical for most pharma and biotech companies and CDMOs," says Janssen. "Many customers we work with developing HPAPI products are small or emerging biotech companies, which have developed an excellent product but don't have production capabilities or assets in-house. What they value is access to flexible and scalable manufacturing assets that can serve their specific needs—extending from drug substance into drug product technologies, in an integrated manner—and hopefully grow with them seamlessly toward commercial production as there is increased demand for their product."

During a presentation at the 2019 CPhI North America conference, however, audience members indicated current capacity may not be able to handle future demand. Anil Kane, executive director, global science and technology, pharmaceutical development services, at Thermo Fisher Scientific, suggests it might be all about planning (see **Sidebar**). "In my opinion, there is capacity [for development-scale and commercial-scale], but of course the infrastructure is limited, so it's all about planning and scheduling," says Kane.

According to Bradbury, there are 209 facilities across 148 companies in the US that offer containment capabilities. Europe has 403 facilities in 247 companies. "All of the evidence indicates that containment facilities are in high demand, and this trend will increase as the oncology pipeline continues to flourish," says Bradbury. "CDMOs with containment capabilities are likely to be at an advantage compared to those without, as the number of marketed HPAPIs tends to increase over time as more HPAPI drugs gain approval," says Bradbury.

To meet this demand, CDMOs may need to tailor services and facilities for specific clients and add facilities, equipment, and services to meet demand. These organizations may also have to balance manufacture of HPAPIs alongside non-potent APIs. Being flexible and tailoring manufacturing techniques, equipment, and containment options to a molecule's properties and synthesis requirements may result in increased safety, a reduction in cost, and enhanced capacity for HPAPIs (1).

Expansion and investment

Contract manufacturing organizations (CMOs) that offer containment capabilities have an advantage over those that do not and may also see an increase in revenue, Bradbury says. "There is a direct correlation between CMOs that offer HPAPI capabilities and generation of high revenues; as those facilities/capabilities are very expensive to build or acquire, only the largest CMOs can afford them, allowing those CMOs to take on projects that others cannot, therefore boosting revenues," says Bradbury. Many CDMOs and CMOs, as a result of the increase in demand, have been making investments in the HPAPI area.

"As we continue working with customers to develop and commercialize these medicines, we are always looking to enhance and expand our capabilities and manufacturing capacity to continue to meet their needs," says Janssen. Lonza announced on June 13, 2019 plans to add two production lines in an expansion of the company's HPAPI capacity at its Visp, Switzerland site (2), which houses the company's Center of Excellence for HPAPI Manufacturing.

The announced investment adds two 4-m^3-scale, multipurpose lines to the company's existing capabilities for lab- to large commercial-scale HPAPI production. The new lines are expected to be online by July 2020. Janssen states that a long-term manufacturing agreement Lonza reached with AstraZeneca was one of the reasons for the investment. In addition, he states, the expansion allows further improvement of flexibility in existing production lines, to reduce time-to-market and accelerate approval timelines for partners.

Another expansion Lonza made at the Visp facility took place in October 2018. The company built HPAPI capacity for the specific support of antibody-drug conjugate (ADC) payload manufacturing (3). "We are seeing an increase in projects in the highly potent API space, including ADCs, and we anticipate that additional capacity at larger scales will be necessary in the near future. This expansion offers companies a seamless integration to our ADC development

FIGURES COURTESY OF GLOBAL DATA.

and manufacturing suites in Visp, that from 2020 onwards will be the first site worldwide where all components to this type of product (i.e., antibody, payload, and conjugation to final product) can be served. We are always seeking ways to better serve our customers of all sizes and help bring innovative life-saving drugs to market," says Janssen.

On June 20, 2019, CDMO Piramal Pharma Solutions announced the opening of a new wing at its Riverview, MI, site, into which the company has invested $10 million to upgrade (4). The new wing will produce HPAPIs with low occupational exposure limits (OELs).

The upgrade includes a new quality control (QC)/analytical lab and two kilo-labs in addition to a doubling of the office space to support growth at the Riverview site. To date, the site has had "the containment capability and engineering controls to safely handle HPAPIs with OELs down to 1mcg/m^3, at scales ranging from grams to ~250 kilos," according to the company. The new wing, with its two kilo-labs and QC/analytical lab, strengthens the company's position in this area. The new wing is designed with "the required engineering controls and containment solutions to handle HPAPIs with OELs <1mcg/m^3 and as low as ~20ng/m^3." Materials will be produced in this new wing at kilo-lab scales; and amounts of <5 kilos can also be produced.

"This new, enhanced capability opens the site up to a new base of customers, including the antibody-drug conjugate market. We are equipped to offer ADC customers a seam-

Ensuring manufacturing of HPAPIs under safe conditions

Pharmaceutical Technology spoke with Anil Kane, executive director, global science and technology, pharmaceutical development services, at Thermo Fisher Scientific about the industry's need for more capacity in the manufacture of highly potent APIs (HPAPIs) and how contract development and manufacturing companies (CDMOs) can ensure they are developing and manufacturing HPAPIs safely.

PharmTech: In your presentation at CPhI North America 2019, one of the questions from the audience was about capacity challenges for HPAPIs. Can you talk a little bit about that?

Kane: The question that came up from the talk was about capacity and having access to contained equipment, facilities, and infrastructure in the industry to support manufacturing. In my opinion, there is capacity [for development-scale and commercial-scale], but of course the infrastructure is limited, so it's all about planning and scheduling. The contained pieces of equipment infrastructure to handle highly potent compounds is not available at many places. There are a few CDMOs that can offer a wide spectrum of contained process trains for manufacturing drug products. At Thermo Fisher, we have continued to monitor the demand for HP compounds both on the API side and the drug product side and are planning ahead to invest into contained equipment to be able to support the pharmaceutical industry.

If clients see the need to handle a specific compound in a certain contained manner, it is good to talk early [and] plan ahead, simply because some of the newer investment and contained equipment also has a long lead time. So, even if we start discussing the need, there is a lead time for the manufacturer/vendor to make this equipment and then to qualify and bring it up and running for the actual use for manufacturing. Again, this is beyond the existing equipment infrastructure and capacity, if there is a special need. There is always the possibility to discuss in partnering on investment, co-investment, and different business models that have been successful within Thermo Fisher, and I'm sure elsewhere as well. The point being [is to plan] ahead and make sure we have the right capacity at the right time, because no customer will like to wait or has the time to wait for 6, 9, 12, or in some cases 18 months to have the infrastructure up and ready, the same with equipment, whether its small scale or commercial scale.

For commercial scale, I would say there is always that time for planning, but for early phase, speed is of the essence to confirm proof of concept and proof of efficacy where only clinical results are key to understand the potential that a molecule has to offer.

PharmTech: Has Thermo had some recent expansions in this area?

Kane: Yes, absolutely. In the oral solids area, where the risk of containment of HP products is higher, we have continued to invest in the infrastructure like contained process trains (e.g., contained encapsulators, contained tablet presses, contained roller compactors, etc.). In the past two to five years, we have continued to invest at several of our facilities across the network. We have also seen an increase in highly potent compounds on the injectables side; however, on the injectables side, the risk is rather less because it is in a liquid format and everything is sterile and contained, so the challenges are less in terms of having multiple process trains in injectables.

PharmTech: Are these equipment installations new technology to handle HP or are you adapting existing?

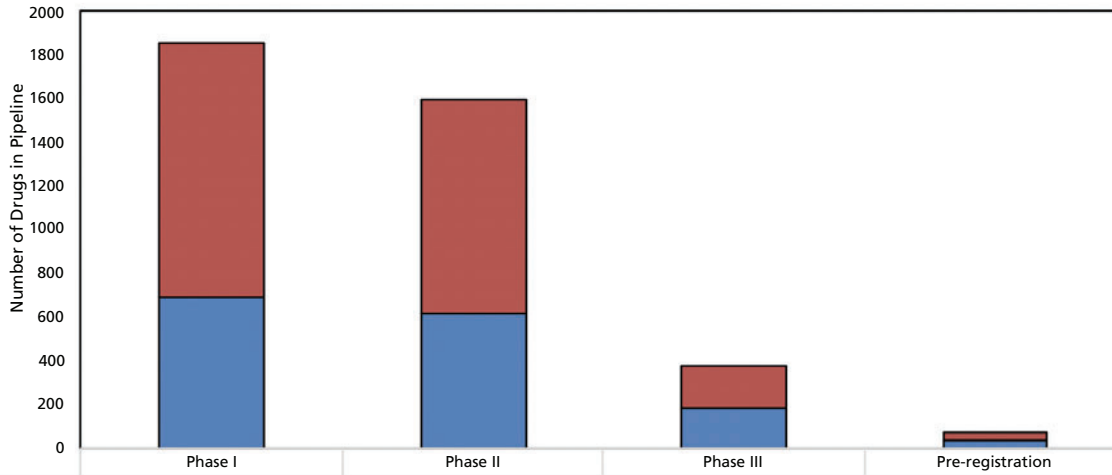
Kane: It's more adapting the existing equipment to have contained solutions to prevent the exposure to personnel operators. It takes a little more time to set up this equipment because the access to such equipment is limited to the purpose they are built, but they do provide protection to the operator from a HPAPI handling perspective.

PharmTech: Do you see any emerging technologies or automation to further separate the person from the process?

Kane: Oh absolutely. Continuous manufacturing is a great solution; however, this comes into interest for the pharmaceutical industry later in the development chain or beyond clinical proof of concept. In continuous processing, everything is a closed loop. There is no operator intervention or a break in the process. There is no potential for exposure between multiple unit processes, so that is one solution. However, there are limitations. Not every product or process can be manufactured under continuous processing based on the stage of the project, the type of the project, etc. The other solution we have adopted for several years now for HPAPIs is vacuum transfer systems between unit processes. This is not new, but not very common as well because it takes time to qualify and validate such processes where you have a continuous transfer between the unit batch process equipment, and this then prevents any intervention by the operator or potential for exposure. The material characterization and properties, the process needs to be developed and validated to suit such vacuum transfers to ensure product quality, but such development work can be planned and done up front. Softgel dosage form is another drug delivery solution for HPAPIs, and we at Thermo Fisher have had success in containment of potent solids in switching from oral solid dosage forms to a softgel.

—Rita Peters

Figure 2: Oncology drugs in development.



	Phase I	Phase II	Phase III	Pre-registration
Other molecule types	1159	972	191	36
Small molecule	692	620	183	40

Source: GlobalData Drugs Database (Accessed date: July 1, 2019)

less end-to-end solution, since we can develop the HPAPI payloads and linkers here in Riverview, send them to our site in Scotland for the antibody conjugation, then back to our Lexington, KY, site for sterile fill/finish," added Vince Ammoscato, vice-president and Riverview site head, in the press release.

In April 2019, Cambrex completed construction of a $24-million HPAPI manufacturing facility in Charles City, IA (5). "The production area will operate to an OEL down to 0.1µg/m^3 and contain four reactors ranging from 200- to 1000-gallon capacity," according to the company. The facility will be capable of manufacturing batch sizes up to 300 kg.

"Across our sites, Cambrex has a strong reputation in the handling and supply of potent molecules, and this investment allows us to increase the capacity we can offer our customers," said John Andrews, vice-president, operations and site director, Cambrex Charles City, in a press release. "We have seen an increased number of molecules in the clinical pipeline being designated as potent and highly potent, so having the flexibility within our manufacturing network to scale up with existing customers as projects progress, as well as accommodate new projects, is crucial to meet those market needs."

Conclusion

It's apparent that the contract manufacturing industry is recognizing the increased demand for HPAPI containment capabilities, and companies are making investments and adjusting their services to meet that demand. As the pharmaceutical industry continues to develop complex treatments requiring complex ingredients, the industry will soon know if these adjustments are enough.

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More on HPAPIs

For more on highly potent APIs, visit PharmTech.com to read the following:

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From Data to Information

Agnes Shanley

IMAGE COURTESY OF APPRENTICE.IO

Making siloed data accessible across functions and to contract partners is the first step to facilitating continuous improvement and enabling use of artificial intelligence in manufacturing.

Biopharmaceutical manufacturers have often described operations as data rich but information poor. While advanced analytics and sensors collect more data than ever before, much of it may not be used or shared with the operations that need it most to prevent lost batches and quality or compliance problems. The rise in outsourcing has only intensified the challenge.

IDC Health Insights surveyed 126 biopharmaceutical and pharmaceutical executives in the United States and the United Kingdom and found a significant gap between their need and their strategies for harnessing data (1). More than 98% of respondents said that cross-functional data access was important or very important to their business strategies, and 94% described the ability to apply advanced analytics and/or artificial intelligence the same way. Respondents believed that data access would be crucial to improving overall quality and productivity as well as the return on investment of their R&D investments.

Lack of clear strategy

However, 51% of those surveyed said that they did not have a clear strategy in place to help them reach either of those goals, citing regulatory uncertainty, budget prioritization, and the need for more action from functional operational groups. As Kevin Julian, senior managing director in Accenture's Life Sciences practice, the survey's sponsor, commented, "Important insights that could lead to the discovery, development, and delivery of promising new treatments are too often trapped within the functional silos of ... biotechnology companies" (2).

While some pharmaceutical manufacturers are still using paper-based record systems, a growing number are digitizing processes and making more data accessible in the most accessible context. On a fundamental level, open control systems and a common data structure have helped allow this to happen, according to a recent report (3) from Rockwell Automation, resulting in distributed control systems (DCS) that enable integration using unmodified Ethernet, and allowing two-way communication between enterprise resource planning (ERP) and manufacturing execution systems (MES). Work is underway to improve collaboration in preclinical and quality labs, where good laboratory practices

(GLPs), rather than good manufacturing practices (GMPs), drive operations (**Sidebar,** p. s14) Much progress is being made in the area of batch records, and expanding connections between electronic lab notebooks, laboratory information management systems, MES, and ERP to increase access to information. Augmented reality offers one way to do this at the basic data recording and recovery level.

In addition, according to Emerson Process Management's consultant Johan Zebib, quality review management and review by exception are being used with MES (4). Data historians can also be developed as a point of access, a concept that Eli Lilly has leveraged with its contract manufacturers in medical devices (5). Vendors are offering tools that make this task easier, with applications that use machine learning and other facets of artificial intelligence, allowing users to make connections between data points that might otherwise have seemed unrelated.

Augmented batch records

Apprentice.io has developed augmented reality and database applications that allow users to get feedback as they perform their jobs and to compare equipment performance and different batch runs (6). Contract development and manufacturing organizations (CDMOs) are becoming a more important market for the technology, says CEO Angelo Stracquatanio, using it not only to share data, but for training and troubleshooting in real time. "There are so many silos within manufacturing, and data are not being leveraged at different levels," he says.

In 2019, the company has made improvements to its augmented reality products with augmented batch recordkeeping products that extend batch connectivity to laboratory information systems (LIMS) and electronic lab notebooks (ELNs), allowing inputs to be captured for every batch. Users can analyze process data to compare batch runs and implement continuous improvement programs and analyze specific runs to isolate deviations, Stracquatanio says, leaving an audit train of data that can be mined to decrease variability.

IMAGE COURTESY OF QUARTIC.AI

A growing number of CDMOs are using Apprentice.io's Tandem remote telepresence tool to collaborate with their clients. The Apprentice System also collects voice, picture, and other types of data to create a rich audit trail. "For example, for a single-use filter, one can scan its bar code. Users now know what filter that is and can create an audit trail for it … and put data together in real time, using a hierarchy of importance to present data in a way that doesn't overwhelm the user," says Stracquatanio.

Although use of artificial intelligence is more advanced in clinical, discovery, and research applications, new platforms are targeting manufacturing.

Artificial intelligence

Use of advanced analytics and artificial intelligence (AI) is growing in the pharmaceutical industry (**Sidebar**, p. s15). However, many companies are still at the earliest stages of developing strategies for using it. So far, the technology is farther along in clinical trials and in discovery. Accenture launched INTIENT in May 2019 to focus on discovery, clinical, and pharmacovigilance applications. Amgen has been working with Tata Consultancy Services on a Holistic Lab digital platform using Dassault Systemes' BIOVIA, for process development (7).

However, some vendors are focusing on pharmaceutical manufacturing applications. Quartic.ai, for example, has launched an AI-driven platform to provide feedback to operators and to monitor and improve processes (8). The platform, which includes a data engine, designed to extract data from DCS, quality management systems (QMS), and data historians, as well as a connector that allows disparate software systems to communicate with each other, was designed to be integrated into existing plants and equipment, but Quartic is also working with a pharma company to embed the platform into a new facility.

Quartic.ai cofounder and CEO Rajiv Anand has an extensive automation and reliability background and previously worked at Emerson. The company's management team members all come from pharmaceutical and automation backgrounds. "We didn't want pharma users to feel that they needed to be coders or data scientists," says vice-president of life sciences Larry Taber.

Levels of digital maturity

The platform (shown in action at a pharmaceutical facility, **Photo,** p. s13) is geared to the fact that every potential user

will have a different level of digital maturity, says Anand. Once legacy data sources have been connected, the artificial intelligence engine can be used to solve a specific problem (e.g., monitoring an asset's performance for deviations), he adds. Some clients are using it for complex predictive work. .

The company has used its platform in a number of situations, including an effort to monitor and improve fermentation yield in a highly variable process where all critical quality attributes were under control. Quartic extracted data and identified a few key batches, Anand explains, and then built an algorithm to study relationships between the batches, clarifying eight years' worth of data and fingerprinting each phase of the process. Ultimately previously unknown sources of variation were discovered. Work will now focus on learning more about them. The company has also done work with pharmaceutical companies in the area of predictive maintenance. Anand recalls one project designed to baseline the performance of an autoclave.

The equipment was modeled and industrial Internet of Things (IIoT) sensors used to get additional vibrational and ultrasound information. Once deployed, machine learning models could then predict potential failures with the ability to trace the source of the failure down to an individual component (i.e., a damaged valve).

GLPS: BETTER DATA ACCESS NEEDED TO IMPROVE COMPLIANCE

Like many crucial regulations, good laboratory practices (GLPs) were enacted in 1979 after FDA observers found serious problems in documentation, training, and data integrity at a number of US research labs (1). Decades later, regulators still find deficiencies in the way that some companies' labs approach data integrity, training, and standard operating procedures (SOPs).Another major problem is reproducibility. According to the Global Biological Standards Institute (GBSI), 50% of published preclinical research cannot be reproduced, a problem that results in product development delays and wastes $28 billion/year in the US alone (2). Culprits were found to be biological reagents and reference materials, study data, and lab protocols.

A number of tools are being developed to help lab scientists capture and use more data, for example, LabStep, an interactive digital platform designed to help scientists get around some of the deficiencies of electronic lab notebooks (ELNs) and refer directly to protocols, SOPs, and other important data (3).

LabTwin introduced a new voice-activated lab assistant at BIO 2019 in Philadelphia. Combining artificial intelligence, voice recognition, and machine language, the hands-free device allows researchers to document steps taken and save explicit details that cannot currently be saved in ELNs (4).

Ultimately, compliance depends on following best practices. Stuart Jones, regulatory quality assurance professional in good laboratory practice (RQAP-GLP) and director of quality assurance at PPD Laboratories' Bioanalytical Laboratory shared recommendations with *Pharmaceutical Technology.*

PharmTech: What are GLP's biggest challenges?

Jones: Because we work in such a regulated environment, a seemingly minor matter can have a significant impact on quality. As such, training is an important best practice, from the time of hire, to retraining when a deviation occurs. Annual refresher training as well as specific group remedial training also should be provided when needed. Meanwhile, the use of automated or electronic systems, such as ELNs, can be especially beneficial in maintaining the most accurate documentation.

PharmTech: How do you recommend that companies tackle training?

Jones: Initial training, especially with newer employees, can be done through reading, lecture, and/or some type of knowledge or learning assessment, but the best results occur when that theoretical work is followed up and supplemented by hands-on training. This is accomplished most effectively by teaming new employees with experienced staff using training goals established within a predetermined curriculum. Some measure of refresher training should be required on at least an annual basis and it should be consistent across all experience levels. Metrics around unplanned protocol and SOP deviations, as well as human error, should be used to gauge the effectiveness of training plans.

PharmTech: What best practices do you recommend to make data less siloed and more accessible to those who may need it (e.g., on cross functional teams working at the same company or facility?)

Jones: One of the best ways to establish a more cross-functional approach and enhance data accessibility is to use one system across all sites. If one across-the-board system is not a possibility, then the multiple systems must be able to work in tandem. Data portals and SharePoint sites also can be utilized to securely share information on a real-time basis.

PharmTech: Reproducibility is a problem for preclinical research. Is that also the case for quality control labs? What do you recommend?

Jones: We have found that, after research and development of the method by our scientists, it is important to involve the sample analysis team in performing some, if not all, of the validation experiments, with technical assistance provided, as needed, by the R&D scientists who developed the method. This approach allows for a shared collaboration between the research and production teams, and continues into sample analysis to ensure reproducible results from the developed and validated method. Best practices include following the proper bioanalytical method validation guidances, the bridging of critical reagents, analyst method qualification, and scientific expertise/knowledge of the assay, as well as the use of incurred sample reproducibility testing.

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—Agnes Shanley

Predicting quality events

There are many other applications where artificial intelligence could be applied to pharmaceutical manufacturing operations, particularly in visualizing end-to-end processes. As data analyst Jonathan Lowe (9) found at one company, more than 100 quality events were being investigated at any one time, stretching staff capacity. A machine learning model was designed to predict which events would take the longest to resolve. The model predicted more than 85% of the severe delays weeks before they happened, allowing quality managers to prioritize tasks more equitably.

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USE OF AI IS GROWING IN PHARMA

Research studies suggest that artificial intelligence (AI) is becoming more widely used within the pharmaceutical industry, and that senior executive support will be crucial to piloting and implementing AI-based approaches to improve R&D efficiency. Industry interviews and an extensive survey (1) by the Tufts Center for the Study of Drug Development (TCSDD), the Drug Information Association (DIA), and eight bio/pharmaceutical manufacturers, has found that pharmaceutical and biopharmaceutical companies are adopting artificial intelligence to help improve functions ranging from discovery and development to risk assessment, safety monitoring, and manufacturing. The research involved interviews with AI experts within the industry, as well as a survey of 402 professionals at pharmaceutical and biopharmaceutical organizations, to assess the current state of AI use and implications for the future.

Survey results found that 70% of respondents use AI in some form, with planning and piloting efforts focused mainly on clinical trials (i.e., patient selection and clinical study recruitment) and identification of data gathering for medicinal products. Research found that staff skills (55%), data structure (52%), and budgets (49%) are currently the greatest obstacles to increased use of AI in pharma. Nearly 60% of survey respondents said that their companies plan to increase staffing over the next two years, to support AI use or implementation.

In addition, TCSDD reports, the survey found that:

- The clinical operations function makes the highest use of AI (61%), followed by pharmacovigilance/safety/risk management (57%), and information technology (IT) (55%).
- 42% of respondents reported that AI implementation is not centrally managed at their companies, while 20% indicated that it is managed by R&D and 12% said that it is overseen by the chief information officer.
- 59% of respondents plan to expand AI staff through 2020, with the largest staffing increases slated for data scientists, computer scientists, IT specialists, and AI architects.

"Pharmaceutical and biotechnology companies as well as service providers now rely on AI technologies across all therapeutic areas,," said Mary Jo Lamberti, research assistant professor and associate director of sponsored research at TCSDD. She expects precision medicine and demand for new rare diseases treatments to drive potentially exponential growth in the industry's use of AI as regulators and industries develop standard policies and regulations to address ethical use, bias, and validation.

Deep Knowledge Analytics released a report that looked at practices at 50 pharmaceutical companies to identify leaders who are most actively driving the use of AI in their organizations (2). The goal is to benchmark the impact of management support on the use of AI, and overall efforts to increase R&D efficiency, according to Margaretta Colangelo, managing partner at Deep Knowledge Ventures. She expects to find a correlation between level of commitment to AI, and market capitalization growth.

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—Agnes Shanley

Why Dread Your Next FDA Inspection?

Charles Spillman

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Performing a compliance gap assessment and focusing on six key factors in your facility's process definition and controls can help your facility pass its next FDA inspection with flying colors.

FDA's close oversight of the pharmaceutical industry through current good manufacturing practices (cGMPs), audit requirements, and rigorous approvals provides patients with a high measure of confidence that medicines and vaccines in the United States are safe and effective. But for those responsible for pharma manufacturing operations—which includes ensuring the performance and reliability of critical equipment—FDA audits can inspire worry. Often, FDA compliance requirements must be balanced against a company's need to compete in an increasingly competitive global market full of treatment options and price sensitivities.

As in most cases, an ounce of prevention—grounded in self-knowledge and organizational awareness—is worth many pounds of cure. Any facility and company can benefit from taking a deep dive into evaluating its readiness for an FDA inspection.

When FDA finds that a pharma manufacturing facility is out of compliance with any part of the required standards for cGMPs, the agency steps in and takes action. This action may range from coaching to help the firm come into compliance to closing and condemning the facility, with many degrees of corrective measures between those two extremes.

FDA may issue a 483 or warning letter that describes any violations that inspectors found during their audit and the steps needed to address each area of concern. It then becomes the facility management's job to determine what went wrong and how best to address each issue, and to document each remediation step in a response to the agency.

Setting (or adjusting) your facility's compliance roadmap

The first prerequisite for success is knowing the areas that FDA auditors will focus most closely on and how to avoid potential inspection pitfalls. Having clear, concise procedures, with practices grounded in sound engineering and rigorous reliability practices, is crucial to avoiding problems. Documenting and demonstrating adherence to these practices is equally important. Because there are so many proprietary processes specific to each individual pharma production facility, details of the processes may be entirely different from one location to another, making the impor-

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tance of good documentation and adherence to methods and established procedures even more critical.

Work management is more than simply utilizing a work order system; it includes constant and deliberate examination of the sources and remedies for recurrent failures, training on the use of non-destructive technologies, documentation and record keeping ... as well as metrics.

Know (and address) your weaknesses

Organizational assessments, both internal and external, are the next step on this path. Knowing where a facility is in relation to the regulatory requirements and guidelines is crucial to success. A tool that is gauged to critique organizational capability, impartially, will provide a platform from which to perform a gap assessment, to examine current performance, and determine what the facility may need to work on in order to achieve compliance with cGMP regulations. This assessment must then be followed by a plan for action (and remediation, if needed), if the firm is to ensure that its next FDA audit is a success.

A number of tools are available to help measure key performance factors that affect regulatory compliance and organizational performance. They include:

- Reliability-centered maintenance (RCM) (1)
- Preventive and predictive maintenance (PM/PdM) optimization
- Supply-chain standards from the American Production and Inventory Control Society (APICS) now known as the Association for Operations Management
- Generally Accepted Accounting Principles (GAAP) financial guidelines
- Failure modes and effects analysis (FMEA)
- Root cause failure analysis (RCFA) methodology.

Using these tools will tell show where a facility's operations are, in terms of regulatory compliance. Whichever assessment tool a company chooses to use should not only give a clear understanding of where the facility currently is, but also form the basis for an action plan designed to improve its competitive position.

This plan should be based on the six crucial aspects of process definition and control:

- Asset management
- Process control
- Documentation management
- Work management
- Supply chain control
- Organizational development.

Asset management is made up of the processes and disciplines that ensure that the facility's production and other physical assets are correctly installed, supported, and documented in a correct equipment hierarchy, in a computerized maintenance management system (CMMS) and on current and correct piping and instrumentation diagrams (P&IDs). Asset management also covers the disciplines and systems that ensure that appropriate preventive and predictive maintenance and other activities are in place to preserve the lifespan and capacity of those assets.

Process control is the system of manufacturing instructions, recipes, and safeguards that any pharma production facility will use in the production of commercial products. The critical control attributes will always be consistency, accuracy, and purity for the product array.

Documentation management has everything to do with the way the organization defines itself, its processes, and the records that it must keep to demonstrate adherence to production standards and maintenance requirements. This will require strict policies for version control, a controlled data repository, and on-going employee training in how to perform standard operating procedures (SOPs) to meet regulatory requirements.

Work management is more than simply utilizing a work order system; it includes constant and deliberate examination of the sources and remedies for recurrent failures (i.e., bad actors), training on the use of non-destructive technologies, documentation and record keeping for regulatory authorities, as well as metrics that measure effectiveness, efficiency, and integration with all stakeholders in the facility.

Supply chain control is made up of those disciplines that are needed to ensure that maintenance, repair, and operations stores are kept in an appropriate environment and stocked at adequate levels to meet demand, and that appropriate security measures are in place to protect works-in-progress and finished products within the facility.

Organizational development is everything that the facility needs to ensure that the staff and management of the firm reach or remain up to date in learning, process optimization, and research and development.

One pharma facility's assessment

In a recent project, this six-factor approach was used to analyze one pharma client's inspection readiness. The company had received a 483 inspectional observations report from FDA, which detailed conditions and findings that put the facility at risk of receiving more severe regulatory citations

Figure 1: An excerpt from the client's readiness assessment survey.

	Always	Usually	Sometimes	Occasionally	Never
Planners are prepared to do field investigations, and prepare appropriately detailed plans for the execution of maintenance work.					X

in the near future. Initial assessment of the facility found a number of problems (e.g., database errors and deficiencies; work management process and PM/PdM issues).

Preliminary assessment

To get a clear picture of how well the organization was managing its procedures and documentation, a five-stage response format assessment tool was used. Responses were assigned a Likert-scale value (2) and tabulated to provide a numeric score for each of the areas that were examined.

Based on the assessment and subsequent discussions with site management, the team undertook a broad-based program of process remediation.A representative response for this client is found in **Figure 1**. The primary components of our program for this client included:

- Walkdown/field verification of assets
- Construction of the asset hierarchy in the resident CMMS system
- Corrections/additions to the plant piping and instrumentation diagrams (P&IDs)
- Risk assessment for all GMP-associated assets
- PM/PdM optimization for all high-value and process-related assets
- Work management system revision.

Diving deeper: data collection

After the above assessments were completed, a data-collection tool specific for the facility was designed, then staff was trained to use the tool. Staff members were assigned to physically inspect and collect data in different areas of the facility based on each area's accessibility and order of importance. Some areas were only accessible during shutdown and had to be scheduled around cleaning schedules.

As audits of each area within the facility were completed, the plant's assets were ranked based on associated equipment and the importance of their placement in the sequence of production operations. Each significant asset (including all instrumentation and control devices) was examined for impact on the process and products.

Based on pre-determined criteria, each asset was assigned a risk value. This value was later used to identify the level of preventive and predictive maintenance support that wold be most appropriate for that asset.One of the primary concerns in performing the walk-down effort was to standardize the level of detail being gathered in the data-collection tool, and to ensure that all of the CMMS data entry was kept current with the field efforts. Omissions and errors in the P&IDs were noted and referred to site engineering for correction on a system-by-system basis.

The work management process was examined and, in cooperation with site engineering, was revised to ensure that all portions of the process were addressed. Specific responsibility, accountability, consulted, and informed (RACI) matrices (3) and processes were designed and documented for:

- Preventive and predictive maintenance generation
- Planning
- Scheduling
- Maintenance, repair, and operations (MRO)management, including bag and tag staging
- Assignment
- Execution
- Documentation
- Close-out
- Metrics development.

All of the activities were controlled from within the resident CMMS system.

Improvement outcomes

Since these efforts, the facility's production has stabilized. Fewer batches are being held for inquiries, and there has been a marked reduction in downtime associated with equipment failure. As a result, the FDA 483 has been lifted, and the facility is in a better position to avoid regulatory noncompliance issues in the future.

Management and employees now embrace a rigorous process for introducing and documenting new assets into the facility's process hierarchy. In addition, since the project was completed, workers have a much better understanding of the roles that they and their colleagues play within the facility, resulting in better communication and cooperation between departments. Documentation of predictive and preventive processes has improved, and standard work plans are being used where needed. The facility is now positioned to adapt for the future, provide safe and reliable products to market, and improve training programs for employees on the SOPs that are required to run the plant in a compliant manner.

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Designing Phase-Appropriate CMC Analytical Programs

Wayland Rushing

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A one-size-fits-all strategy is not the best approach for the development of a chemistry, manufacturing, and controls (CMC) program. Company goals, budget, staff capabilities, drug type, and development phase factor into building an effective CMC program.

The landscape of drug development has continued to shift over time. Just a few decades ago, most drugs were developed from beginning to end by large pharmaceutical companies with well-defined systems of control. Today, this has significantly changed; much early development (Pre-investigational new drug [IND], Phase I, Phase II) work is performed by small- to medium-size companies, many of which are virtual companies.

The goals, drivers, and challenges encountered by these smaller companies are significantly different than their larger counterparts. Instead of an end goal of commercializing a new drug, the goal may be to generate the appropriate interest to sell the intellectual property or company. Instead of a large team of experts who are responsible for the various analytical requirements, the responsibility falls to a few individuals, and in many cases, just a single person. As a result, smaller companies commonly rely on the expertise of contract laboratories to perform analytical work, act as partners in the development process, and help design the appropriate chemistry, manufacturing, and controls (CMC) analytical activities that will meet their company's specific goals.

The challenge for designing these CMC programs is that each becomes a custom program; there is no one-size-fits-all model to be applied. A unique combination of drivers must be considered when designing an appropriate program.

Funding and CMC

For many small or virtual companies, funding is a primary driver for decision making. This can often lead to conflicts between what testing "should" be done versus what "has" to be completed. It is not uncommon for small pharma companies to encounter one of the following funding challenges.

Milestone funding. Under milestone funding, the infusion of additional development funds is tied to reaching a certain milestone, which releases funds to continue development. With this approach, companies may focus efforts on attaining the funding milestones rather than regulatory or development drivers. In these scenarios, studies that may be required for regulatory approval or studies that would aid in the longer-term development goals are postponed for a later point in favor of studies that will achieve the next funding milestone.

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Limited funding. In a limited funding scenario, which can impact both small and large companies, the analytical development functions are given a finite amount of funding that cannot be exceeded. With limited funding, companies may design programs that focus on obtaining the bare minimum requirements, while delaying or foregoing work that may be beneficial in the longer term. This process can be summarized as the conflict between the "nice to have" studies versus the "have to have" studies.

Regulatory guidance?

Regulatory guidance for early-phase analytical CMC support is limited. FDA and the International Conference for Harmonization (ICH) have several guidances that can be used to design the program to meet expectations, including FDA's *Current Good Manufacturing Practice for Phase 1 Investigational Drugs Guidance for Industry* (1), *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drug, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products* (2), and *INDs for Phase 2 and Phase 3 Studies Chemistry, Manufacturing, and Controls Information* (3); and ICH Q7, *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients* (4).

These guidances encourage the use of a phase-appropriate approach and provide a basic foundation for expectations of what is appropriate for different clinical phases of CMC analytical programs. It is not uncommon, however, to find pharmaceutical companies and contract research organizations (CROs) that are not taking advantage of the phase-appropriate approach and simply reference the typical ICH guidances for analytical items, such as method validation (5) or stability (6), when the guidances are not meant to be applied to early-phase support.

There are two reasons why companies take these steps. First, while the FDA guidances encourage the use of a phase-appropriate approach, they lack specific details of the actual requirements. As a result, companies may prefer to reference the quantitative requirements held within the ICH guidances as a conservative approach. A second reason may revolve around the possible difficulty in implementing a CGMP quality system that allows for differing levels of CGMP compliance throughout the various clinical phases of development.

The development goals of many smaller or virtual companies stop short of commercialization. Many companies know they will not have sufficient funding to support commercialization of their product. They adopt a development strategy to bring the drug to a certain point within the development cycle (i.e., Phase 2A), then enter into a co-development agreement with a larger pharmaceutical company or sell the company (or the drug) to another company to continue the development. In these scenarios, the focus may not be on the regulatory requirements or long-term developmental needs, but rather the studies and data required to entice a partner or buyer.

These various drivers for the smaller pharma companies are not only complex but, in some cases, may conflict with another driver. This strategy often complicates the design of an appropriate program. To design the program, it is important to understand the typical analytical CMC activities and their limitations and challenges.

Analytical methods to test pharmaceuticals must be "fit for their intended purpose" (7). Method developers evaluate the intent of the method's purpose prior to starting any development work by asking if the method is for assay or impurities, if the method needs to be stability indicating, and if the testing is for an API or drug product.

Additional questions that are important for the early-phase work include the phase of product development and if the synthesis or manufacturing routes are finalized.

Stability testing example

The development of stability-indicating methods can be expensive and lengthy, leading to the question of whether such testing needs to be performed for early-phase clinical materials.

Consider the example of a Phase I API in development. The current synthetic scheme is used to produce 1 kg of material. While this amount is sufficient for Phase I, the scheme will have to be scaled up and optimized for Phases II and III, which will likely result in a new impurity profile versus the Phase I material. For the Phase I material, only two batches are expected to be produced.

Do pharma companies need to spend the time and effort to develop—and validate—a stability-indicating method knowing that it may likely need to be redeveloped after being applied to only two batches of API? Unfortunately, many pharma companies that have taken a conservative approach and answered "yes," wasting time and money when they had to redevelop the method to address changes.

For the phase-appropriate approach, method development should start as early in the process as possible; however, developers should understand the intent of the method is to be applied to early-phase material in addition to the normal "intent of the method" questions. Using this principle will allow for efficient method development with reduced costs and time.

In many cases, applying a generic high-performance liquid chromatography (HPLC) method may suffice during Phase I and early Phase II until more is known about the compound, and the synthetic and manufacturing routes are final.

Once developed, the method must be validated to demonstrate that it is fit for the intended purpose. ICH Q2(R1) (5) and *United States Pharmacopeia* <1225> (8) provide specific expectations on what elements are required for Phase III and commercial materials; however, this level of validation would be wasteful and detrimental to an early-phase development program. The analytical

characteristics often included in the registration validation include the following:

- Accuracy
- Precision
- Intermediate precision
- Specificity (including stress studies as applicable)
- Detection limit
- Quantitation limit
- Linearity
- Range
- Robustness
- Solution stability.

As with method development, it is important to evaluate the development drivers in regard to the program. What attributes would be needed to ensure that the method is fit for purpose as applied to an early-phase program? The answer will vary depending on the specifics on the product and application of the method.

FDA's Phase I guidance states that the analytical methods "should be scientifically sound (e.g., specific, sensitive, and accurate), suitable, and reliable for the specified purpose (2). The Phase II guidance does not list specific criteria but only states that "appropriate validation data should be available" (3). While some of the attributes would be applicable to early-phase programs, others would not need to be applied until later in the developmental cycle. Therefore, a pharma company can develop a phase-appropriate validation that not only serves regulatory expectations, but also allows for conservation of resources to be applied to other activities or held until later in the developmental cycle.

A phase-appropriate validation for a Phase I material could then be designed around the following elements:

- Accuracy
- Precision
- Linearity
- Specificity
- Detection limit
- Quantitation limit.

Stability studies are perhaps the most expensive and time-intensive portions of analytical support during drug development. The studies can cost more than $100,000 and take years to complete. While the regulatory requirements for stability for commercialization are well defined by the ICH Q1 guidances, they are not practical given the drivers for early-phase programs. Again, FDA gives limited guidance on the expectations.

For Phase I materials, the guidance states that a stability study should be performed "to monitor the stability and quality of the Phase I investigational drug during the clinical trial" (2). The minimum requirements would then translate to performing a stability study to cover the length of dosing the drug that will be used in the clinical study (i.e., If the clinical study is one month long, the stability study would only need to cover that length of time). In many instances, stability studies are performed in conjunction with the clinical trials, with the initial time point being conducted prior to starting the clinical study and the final time point being conducted after the date of final dosing. This approach does minimize the total cost expenditure for the stability study and may be beneficial for those companies with funding constraints. It may be beneficial to continue the stability studies beyond the dosing timing to gather additional development data useful in the longer-term developmental goals of the product.

For Phase II material, the guidance does not provide additional guidance beyond that offered for Phase I, stating that a description of the stability performance to support clinical studies should be submitted. The only difference here is that when moving into Phase II, it is expected a company would have already generated stability data to support its clinical dosing timelines prior to initiating the studies.

Conclusion

Designing a phase-appropriate CMC analytical development strategy can be crucial to the success of a small or virtual pharma company. The successful program will balance various drivers to provide a program that meets the overall development goals without sacrificing the requirements of the program. A successful strategy cannot be accomplished with a one-size-fits-all model, but rather requires evaluation of the company's individual drivers and goals along with the specific requirements of the compound being developed.

Given that these companies typically rely on CROs to help guide this decision-making process, it is crucial for the pharma-CRO relationship to be a true partnership in the developmental process. This level of relationship requires that the CRO be more than a simple testing laboratory and be a partner/consultant with the pharma company to design the programs.

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Best Practices for Selecting a Service Provider

Jiawei Chen

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Key considerations when searching for an analytical service provider include workflow, hardware, and regulatory support.

The right service provider can be crucial to maintaining and expanding a laboratory's workflows. Finding the best instrument for the lab's needs, along with the right service plan, can be a time-consuming process. Investing this time at the point of purchase can result in a world of difference in a laboratory's capabilities for years to come.

For each individual lab, there are a number of key considerations to think through to make sure the service provider and their instruments provide value and maximize lab operation, output, and return on investment. The greatest value is through quality and reliable support that will maintain or improve workflow productivity year after year.

Uptime vs. costs

Laboratory equipment and routine servicing can be expensive, particularly with mass spectrometry (MS) or liquid chromatography (LC)–MS when compared to other instruments in the lab. When making this level of investment, it is important to look beyond the cost and consider the value or impact the instrument or service may provide.

The choice between uptime and cost is a strong determining factor when making a purchase. Uptime deals with the duration the instrument needs to be in use, as well as the duration that one can afford to lose to disruption, and cost is the money one is willing to spend to avoid the disruption. Depending on the specific needs of the laboratory, some may weigh uptime over cost or vice versa.

In high-throughput analytical labs where thousands of samples can be processed daily, losing a single day to malfunctioning equipment is a major setback. In these cases, uptime is prioritized over cost, and a higher premium service plan that offers prioritized support is needed. On the other hand, in some academic labs where not as many samples are routinely processed, the impact of downtime may be less severe. This situation, combined with budgets that may be smaller, results in cost becoming a greater priority and a lower-level service plan may be more appropriate.

Determining the right balance of uptime and cost is a challenge and can sometimes turn out to be an empirical process. Though some laboratories may opt to go with third-

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party suppliers for their service plan, these laboratories often revert back to the original manufacturer following or even during an incident where in-depth knowledge of the instrument is required. When deciding on the service provider and plan, it is best to talk with dedicated experts who thoroughly know the instruments and are able to clearly explain the benefits and downfalls of each service plan to determine which one best meets the current and future needs of the laboratory users.

A service provider must be proactive in offering workflow support, and can do so by monitoring instruments in real-time.

Workflow support

Traditionally, when thinking through service plans, laboratories only think about when an instrument breaks and how it will be fixed. However, it is equally, if not more, important to think about daily and long-term workflow support.

In the field of MS, research takes multiple years, with a high likelihood that the scope of work changes or expands. Some laboratories may simply need to substantially increase their throughput and workflow accordingly, while others will require more analytical capabilities. Alternatively, the focus of a laboratory may shift from analyzing one type of sample to another type, potentially requiring a radically different application of their instruments. These are only a few examples of how laboratory and customer needs can evolve. Rarely is the same application used day after day, year after year, and finding a service provider that will evolve alongside the laboratory and continue to meet its users' needs is vital.

A service provider must be proactive in offering workflow support, and can do so by monitoring instruments in real-time. Providers are starting to offer remote support and tracking instruments in which operational health is continuously monitored while maintaining the privacy of the operator's data as it is not tracked. This allows the service provider to anticipate and possibly prevent any downtime by monitoring and responding quickly to alarms triggered by fault conditions. Should the selected service plan (where cost is prioritized over uptime) not include the need to raise such a pre-emptive alarm, the monitoring of the instrument can still be useful for ensuring that support staff are alerted automatically to be ready to help resolve the issue.

Constant monitoring of the instruments also allows the laboratory to track their utilization. The laboratory or instrument manager can easily see if the activity levels are within the desired range or if there are any peaks and valleys that could be better balanced to optimize uptime.

The key benefit of continuous monitoring is the peace of mind for scientists in knowing their instruments are functioning properly, and that if an issue arises or is imminent, he/she will be alerted immediately, so that necessary action is taken to resolve or avoid the issue. This facilitates the effective maintenance of a steady and reliable workflow.

Hardware support

An important piece of proactive workflow support is related to parts. Typically, instrument malfunctions are related to hardware when a part or accessory is not working properly. It is important to have a reliable source that will provide new, authentic parts with long-term quality and functionality.

In researching sources for replacement parts or upgrades, there are two options: to go with the original equipment manufacturer (OEM) or a third-party. Similar to service plans, both sources have benefits and disadvantages. OEM parts are new, latest revision and come with a functional guarantee. Though they are more expensive, the OEM usually offers the greatest reliability, quality, and traceability—ensuring minimal disruption over a longer period of time. Third-party sources are more cost-effective, but do not come with the same assurances as an OEM.

The quality and cost of parts work hand-in-hand. It is important to retain additional budget, if it is not already part of a service plan, to maintain or replace parts as soon as possible to minimize any additional damage resulting from malfunctioning parts. This will be particularly valuable for older instruments, which may be more prone to malfunction. As an OEM, SCIEX continues to produce parts even if the original instrument is no longer available to ensure the full lifecycle of the instrument is covered.

Investing in hardware—in terms of replacement parts as well as the original instrument—obtained from a trusted service provider is vital to maintaining a productive and fully functional workflow long-term.

Regulatory support

A disruption in instrument performance can be a major setback and potentially detrimental, particularly in pharmaceutical laboratories. Often these labs need to operate in a controlled environment where the instruments (hardware and software) and processes need to be compliant with numerous regulations.

Confirming and maintaining compliance can be a complex, costly, and time-consuming process. Working with a service provider who is knowledgeable about global and local standards and regulatory requirements can help laboratories be well prepared for future audits.

Service providers that have a global footprint offer laboratory access to trained certified engineers from around the world. They are experts in global regulations (e.g.,

good laboratory practice, good clinical practice, and good manufacturing practice) and country-specific regulations, such as US FDA and China's Food and Drug Administration, and will guide laboratories through the installation, operation, performance, re-qualification, and validation processes needed to help ensure the lab is fully compliant.

An audit is also not an area in which laboratories can afford to fail. By working with a reliable service provider with compliance expertise, laboratories will have help ensuring that they will meet all regulatory standards.

The focus of the laboratory will help determine the complexity of instruments and, in turn, the level of training the scientists will need.

Internal maintenance

In addition to receiving support from the service provider, it is important to train laboratory staff to help with everyday instrument maintenance, troubleshoot issues, and problem-solve. This is a key factor in both independently maintaining the lab's workflow and properly communicating with the service provider.

The focus of the laboratory will help determine the complexity of instruments and, in turn, the level of training the scientists will need. Particularly for LC–MS laboratories, where the instruments are sophisticated, intricate, and expensive, a reliably trained team can be crucial to the functionality and success of the lab.

It is beneficial to have basic-level training with each instrument purchase after the instrument is installed that focuses on basic usability and maintenance. To have more detailed training and to tailor the user and instrument to meet the exact needs of a lab, an application scientist who knows the ins and outs of the equipment as well as the particularities of the type of lab will be needed. The level of training required depends on the needs of the lab and complexity of the instrument. For instance, pharmaceutical laboratories that routinely conduct drug or pesticide screenings are likely to need more detailed training to ensure they're meeting the required applications and standards.

Experience has shown, a team that receives regular trainings by the service provider will have an improved and consistent understanding of the instrument, and in turn, yield greater productivity and efficient troubleshooting. In fact, the majority of issues may be resolved over phone or email.

Manufacturer laboratory collaboration

Regardless of whether it is troubleshooting a problem or evolving alongside the laboratory and its uses, the service provider should work with the laboratory as a collaborative partner. Having both parties on the same page will yield greater efficiencies and advancements over time. By partnering in this way with the OEM, laboratories and their users can voice their opinions and inform the direction of new developments and innovation to best serve their current and future needs and preferences.

Greater success is often reported when a dedicated application specialist is assigned to a laboratory. This provides customers with a direct line of communication utilized solely to meet their needs, as well as provides a collaborative partner to better evolve the instruments for future applications.

Through collaborative problem-solving, more solutions are found to aid the growth and development of instruments, hardware, and software. Community formulated frequently-asked question platforms that highlight real feedback, questions, and fixes build a knowledge base for fellow laboratory users to access as well as the service provider to refer to in making improvements.

The greater the collaboration by all party experts—service provider and laboratory users—the greater the speed in finding solutions to problems and in evolving the instrument to better fit laboratory needs.

In the end, these key considerations all come down to finding a service provider that offers seamless workflow support. Laboratories need to look past the immediate support needs, such as 'break-and-fix,' and consider their long-term goals and the level of support needed to achieve them.

From instrument to software and compliance, steady support results in continuous work, minimal disruptions, and a greater confidence in the reliable function of the instruments. Combined, the laboratory will receive greater value from their service provider and so, yield greater success. **PT**

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De-risking Biologics Development Through Advanced Mass Spectrometry Approaches

Jennifer S. Chadwick

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Using advanced HDX-MS and native MS techniques can improve the identification of potentially successful biologic drugs and de-risk CMC and clinical designs.

The overall success of moving drugs from Phase I clinical trials to approval is approximately 10% (1), indicating an enormous opportunity to improve approaches to the development of biologic drugs and more effectively achieve intended clinical outcomes. Advanced analytical assessment of molecular attributes has been demonstrated to enhance the likelihood of success of biologic drugs in clinical development, which has become more important as an increasing proportion of the therapeutics pipeline is made up of biologic drugs. This article discusses how the use of hybrid mass spectrometry (MS) approaches can inform and de-risk decisions to help enable success of biologic development programs (2).

Biologics are large, complex molecules produced in living cells. Therapeutics on the market and in development include monoclonal antibodies (mAbs) and related analogs, recombinant human proteins, enzyme-replacement therapies, fusion proteins, antibody-drug conjugates, bispecific drugs, and a wide array of gene and cell therapy approaches.

The biologic therapeutics class also represents an economically important sector. The total global biologics market was worth $255 billion in 2017 (3) and is projected to grow to between $400 billion and $581 billion by 2025/2026 (3,4). North America alone is predicted to have a revenue share of the market of more than 40% by the end of 2024 (5). The biopharmaceutical industry's investment is growing. In 1980, US members of Pharmaceutical Research and Manufacturers of America (PhRMA) spent $2 billion on biopharma R&D. By 2015, this amount had risen to an estimated $58.8 billion (5).

Biologic drugs offer unprecedented innovation, rapid growth, and major opportunities, both for biopharma companies and for patients, but their successful development can be challenging. Even with the greater knowledge and process improvements put in place since the 1980s, more than 90% of all drug candidates fail between Phase I and approval (1), and over half will fail in Phase III (6). According to an FDA report, there were more than 6300

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biopharmaceuticals in clinical development globally in August 2016 (7). This has increased from 5400 products in December 2011. Of the products in clinical trials, 2660 were in Phase II and only 932 in Phase III, confirming the high rate of attrition (7).

Biologics are costly to manufacture at clinical and commercial scale, and the smallest changes in manufacturing processes can have an impact on drug safety and efficacy. Approaches that inform on critical quality attributes, critical process parameters, and correlations with clinical outcomes can reduce the failure rate and could help to speed drugs through development and ultimately reduce the enormous aggregate costs of drug development.

The disadvantage of high-resolution methods is that they take longer and require greater resources than low-resolution techniques.

Better knowledge makes for better drug development

Understanding a candidate drug and how it interacts with the target across a number of clinically relevant doses improves the chances of a successful transition from preclinical to clinical development. Acquiring as much information as possible at an early stage will help researchers to select the best candidate and corresponding dose, inform the chemistry, manufacturing, and controls (CMC) program, and design better clinical trials. Key steps include defining the binding site profile and target site engagement as well as further understanding the drug's mechanism of action (MoA).

How the candidate drug interacts and engages with its target play a major role in its efficacy and are important markers of success. By creating an accurate profile and gaining a better understanding of the interaction between drug and target, researchers can select the best candidates and further optimize their safety and efficacy. By using the right analytical approaches, researchers can generate insights into drug candidates' molecular and chemical attributes and further develop correlations between these attributes and biological function and/or clinical outcomes, which will further improve candidate selection and optimization.

Gaining a better understanding

Analytical technology is progressing fast, providing researchers with more and better tools to understand biologic drug-target interactions and mechanism of action. There is a wide variety of high-throughput low-resolution methods used to detect the binding between molecules and establish the binding affinities, including the following:

- Surface plasmon resonance (SPR)
- Biolayer interferometry (BLI)
- Analytical ultracentrifugation (AUC)
- Light scattering techniques
- Isothermal titration calorimetry (ITC)
- Size-exclusion chromatography (SEC).

These techniques all allow rapid data collection; however, interpreting the results and applying them to strategic decisions about drug candidate selection can be challenging, if not confounding in many cases. All of these approaches require the analysts to make assumptions while interpreting the data, which can result in variations in the results. For example, calculating the size of biologics using AUC and SEC requires an assumption of the shape of the molecule. If this assumption is incorrect, the size and therefore the stoichiometry may be incorrect. Complexes, which include a number of different components, can further affect the data analysis.

Detailed molecular characterization methods using high-resolution structure tools give researchers access to much greater detail about the interaction between biologic drug candidates and their target sites, right down to the level of the residues and regions directly involved in binding or affected by the binding process. These also provide a better understanding of the impact of components within complexes, and how these can affect the mechanism of action, and the eventual outcomes in vivo and in clinical trials. This level of characterization is further important in CMC to make better predictions of the stability of the biologic molecules as they move from drug discovery to drug development, allowing researchers to make go/no-go decisions or continue the optimization process. Detailed characterization also allows assessment of the quality of in-process materials at every step. At the clinical stage, high-resolution techniques are important to support the scale-up/out process and to ensure that the drug product meets the same specifications when it is produced in larger batches and/or reproduced in different facilities.

The disadvantage of high-resolution methods is that they take longer and require greater resources than low-resolution techniques.

The benefits and applications of MS

MS can be used to assess a wide range of biologic species, across a breadth of properties (see **Table I**). These may be homogenous samples or individual components in heterogenous or complex mixtures. MS is usually performed at peptide-level resolution, but the resolution can be made even higher by using tandem MS (MS/MS) or multidimensional MS (MSn) to further probe specific features of individual peptides. While this process takes longer and uses more resources, it does provide more detailed information on complex systems, including those

Table I: Benefits and disadvantages of common high-resolution techniques.

Technique	Benefits	Disadvantages
X-ray crystallography	• Can characterize complexes at high resolution and show binding interactions at atomic level • Provides useful details about binding interactions to guide drug development • Is not affected by size	• Requires high-quality crystals of complexes, which can be difficult to obtain • Crystals may not always represent the functional form of the molecule • Limited by post-translational modifications
Nuclear magnetic resonance	• Can provide atomic-level detail in solution, which is more physiologically/pharmacologically relevant than crystals • Can identify binding interactions and conformational changes quickly once data are assigned • Amenable to analysis in diverse conditions/formulations	• Assigning data can be challenging, especially with larger molecules such as monoclonal antibodies • Limited by size • Requires stable isotope incorporation
Cryo-electron microscopy	• Can examine shapes and structures of large, heterogeneous complexes • Can show orientation between associated proteins in complexes and aggregates	• Medium resolution • Potential to be altered with surface interactions
Mass spectrometry	• Can be used with highly diverse biologic species having a broad range of properties (e.g., size, glycosylation/modifications, structure, shape) • Robust and fast analysis compared with other high-resolution techniques • Compatible with complex mixtures • Peptide-level and higher resolution	• Adding dimensions increases time required for analysis

that are not amenable to detection using X-ray crystallography or NMR.

The benefits of mass spectrometry approaches include:

- Assessing potential competing effects that diminish efficacy
- Greater certainty of identifying engagement sites correctly
- Showing how multiple target-drug interactions relate to function/MoA. For example, characterizing valency and binding for mAbs/bispecifics
- Elucidating interactions between drugs and the immune system
- Understanding the impact of glycosylation or other modifications on biologic drug stability as part of the CMC decision-making process
- Identifying changes in the biologic drug in different conditions, in complexes, and comparability before/after scale-up to support CMC decisions
- Analyzing synergy and compatibility among therapeutics to aid candidate selection, development, and CMC decisions to support personalized medicine.

The two key MS approaches for characterizing binding and MoA are hydrogen deuterium exchange (HDX) MS and native MS (see **Table II**).

HDX-MS measures the rate of exchange of protons between labile amides and aqueous solution. This analysis approach can map binding site interactions, including epitopes on antigens, paratopes on antibodies, protein-protein/ligand interfaces, and self-association as well as identify conformational changes induced by binding.

Native MS is a gentler technique that determines the size of intact macromolecules, proteins, and complexes while still in their folded state as well as aggregated species. The technique has been used successfully to analyze multi-protein assemblies, viral capsids, and mAb-antigen and protein-small molecule complexes. Data from native MS analysis can confirm the stoichiometry of subunits in heterogeneous complexes, and further MS analyses can help to verify the individual components in detected complexes. An example of this is the determination of the relative levels of correctly paired heteromeric bispecific chains and incorrectly paired homomeric species in the production of a bispecific antibody candidate. An important example application is determination of the level of homotypic anti-CD3 pairings in a bispecific product for assessing potential risk of immune reactions caused by CD3 cross-linking.

HDX- and native MS can both play an important role in strategy and decision-making in drug development and CMC. By mapping interactions between antibodies and antigens, HDX-MS can help researchers re-engineer proteins to optimize their safety, efficacy, stability, and ability to be manufactured. This could include identifying antidrug antibody binding epitopes on therapeutic proteins, showing where proteins change shape upon binding, or highlighting hot spots for aggregation.

Table II: Mass spectrometry (MS) approaches for characterizing binding.

MS approach	Purpose	Information provided	Outcomes
Hydrogen-deuterium exchange MS	Epitope mapping	• Reliably applied to diverse proteins and complexes: o Large, non-globular, flexible o Heavily glycosylated • Identifies regions involved in binding interactions • Identifies regions that undergo conformational change on binding	• Identify sites of target engagement by therapeutic • Assess changes to target induced by binding • Assess anti-drug antibody epitopes for personalized treatment
Native MS	Stoichiometry of complexes	• Exact mass unambiguously identifies number and types of subunits in large complexes • Analysis of solution state • Assess binding of competing species • Distinguish homo- versus heterodimeric bispecific monoclonal antibodies (mAbs)	• Determine whether formed complexes support intended mechanism of action (MoA)
Combined	Improve decision-making	• Potential for informing MoA and efficacy o Co-engagement o Valency o Oligomerization • Identify potential synergies and competition o Combine therapeutics o Assess displacement by native ligands • Assess immune complex structures for potential immune reactivity	• Improve efficacy • Optimize dosing • Understand bioavailability and activity • Reduce counterproductive clearance • Improve stability and reduce aggregation • Reduce potential immune reactions • Enable re-engineering for better optimization and creation of biobetters

Native MS techniques can be used to characterize stoichiometry of non-covalent complexes. By combining this with HDX-MS, researchers can understand more about target engagement and therefore improve candidate selection and optimization, thereby de-risking the development of biologic drugs.

Combining the approaches

While individual approaches can provide a lot of useful data, using a combination of techniques has additional benefits. For example, data from low-resolution approaches can be interpreted much more accurately in the context of high-resolution data. There are significant opportunities offered by using combined HDX-MS and native MS approaches to interpret accurately low-resolution data from high-throughput methods. This allows researchers opportunity to improve development from candidate selection through to manufacturing approaches.

Conclusion

Strategic application of advanced HDX-MS and native MS techniques, alone and in combination with each other and with other analysis approaches, can improve the identification of potentially successful biologic drugs and de-risking CMC and clinical designs earlier. Detailed assessment of target engagement using these techniques may provide useful guidance for better decision-making in biologic development programs.

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Industrializing Cell and Gene Therapies

Agnes Shanley

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Now that the first genetically modified cell therapies are being manufactured, the industry must move beyond "whatever works" to meet growing demand.

In less than four decades, biopharmaceutical manufacturing has traveled light years from its origins in facilities such as Amgen's Building Six in Thousand Oaks, California, which manufactured 200 grams of recombinant human erythropoietin per year with two stainless steel tanks and 3000 roller bottles (1). As increasingly sophisticated equipment was developed for upstream and downstream processing, standardization allowed for the engineering of new processes and platforms and faster development and scale-up.

Cell therapies, genetically modified cell therapies, gene therapies, and tissue engineering now stand where biotech was in the late 1980s; the first products have been commercialized and manufacturing them has become a question of doing whatever works.

"The greatest success so far has been the fact that the industry has even launched the cell and gene therapy products that it has introduced. Regulators have accepted them, and developers have figured out how to get them to the market," says Phil Vanek, general manager of cell and gene therapy strategy, GE Healthcare.

The next phases of industrial development, Vanek says, will focus on streamlining the supply chain and the creation of increased therapeutic value; engineering new therapeutic value into the cells to achieve the highest potency per amount of production time and cost; and connecting both of these efforts, via an intricate pathway, directly to patients.

"We must draw on the valuable experience that we acquired in biologics manufacturing, where we evolved from small to large volumes and from stainless-steel to single-use platforms for flexibility," says Lisa Krallis, head of business development, cell and gene technologies at Lonza Pharma & Biotech.

The pressure is on

As the cell and gene therapy market grows, substantial pressure is on developers to meet commercial demand and supply clinical quantities of material. By the end of 2018, 1028 global clinical trials were underway for cell and gene therapies, 58% of them for oncology therapies; 57% of them in Phase II, and nearly 9% in Phase III, according to the Alliance for Regenerative Medicine's 2018 Regenerative Medicine Data Report (2). That year, more than 906 com-

panies focused on cell and gene therapies, generating $19 billion in merger and acquisition activity and $13.3 billion in corporate financing for research and development, up 73% from 2017.

As the cell and gene therapy market grows, substantial pressure is on developers to meet commercial demand and supply clinical quantities of material.

Meeting increased demand will require a one-to-two-orders-of-magnitude improvement in gene therapy vector manufacturing, and a similar reduction in cost, as Peter Marks, director of FDA's Center for Biologics Evaluation and Research noted at the 2018 Galien Foundation's Forum (3). "Platforms need to become standardized, industrialized for yield, and then optimized for complexity," says Krallis.

Manufacturing platforms

Today, efforts focus on improving existing manufacturing platforms for both patient-specific, or autologous therapies, and allogeneic treatments designed for many patients (4). They include *in-vivo* adeno-associated viral vector (AVV) technology, which enabled the commercialization of Spark Therapeutics' retinal blindness therapy, Luxturna, which FDA approved in December 2017. Roche plans to acquire the company (pending approval by the US Federal Trade Commission) (5).

Also being developed are *ex-vivo* Lentivirus vectors, which modify cells that have been removed from a patient, then are combined with T or stem cells and injected back into the patient, an approach that Bluebird Bio is using for chimeric antigen receptor (CAR)-T cell therapies (3).

Novartis and Kite have developed faster autologous CAR-T processes, while ZIOPharm is refining its Sleeping Beauty non-viral gene transfer platform, which FDA approved for use in T-cell receptor cell therapy in June 2019 (6). That same month, FDA approved the first clinical trials using UCART123, an off-the-shelf, allogeneic cell therapy approach developed by the French company, Cellectis (7) that uses Talen, a proprietary gene editing technology. Trials are already underway for UCART19 and UCART123, other therapies that utilize the technology.

"With queues for new vector production frequently around 12 months, the industry isn't where it needs to be in terms of production capacity," says Andrew Bulpin, head of process systems at MilliporeSigma. "As a result, innovation focuses on improving scalability to enhance the amount of material produced per run." Upstream, the best way to improve scalability is to move cell culture into suspension. "Current vector production is disproportionately done in adherent culture, which is only conducive to scaling out, not scaling up. There is also significant use of serum in cell culture media, which increases regulatory burden and creates a potential supply bottleneck," says Bulpin. Moving culture into single-use bioreactors improves scalability and enables a shift to chemically defined media, solving a number of problems at once, he says.

For downstream processing, Bulpin explains, the picture is more complex because of the number of steps required in the workflow. "In addition to process complexity, there is a need to increase the scale that current unit operations can handle as well as to minimize the loss of vector in each unit operation. Innovations in chromatography and filtration will be important to achieving those goals," he says.

Equipment design

Platforms specifically designed for viral gene therapy applications could address more of these challenges at once and will be essential for ongoing growth in the industry, says Bulpin. At this point, innovative therapies are still being developed in equipment that was designed for traditional biopharmaceuticals, and there is a disconnect. "In biologics, the cell is a byproduct, and material is purified by removing that byproduct," explains Vanek. "In cell therapy, however, the cell is the final product, so we must be very careful to develop platforms and approaches that do not fundamentally change the biology of the cell. That's a tall order," he says.

As more is learned about innovative therapies in the clinic, equipment will eventually be customized for use with cell and gene therapies, Vanek says. "Every cell type will have a set of specific conditions that it thrives under, and those conditions will ultimately be developed into next-generation equipment, whether bioreactors, cell processing platforms, and ancillary materials, upstream and downstream methodologies, including everything from reagents to hardware, to consumables and software," he says.

Allogeneic vs. autologous needs

"In patient-specific therapies, you may not need more than a billion cells per batch, but if you start to scale up in allogeneic you might need hundreds of billions of cells per batch," Vanek says. In order to scale up and increase the volumes of allogeneic cell therapies, manufacturers will need to be able to move seamlessly from adherent to suspension cell culture, says Krallis, and ultimately 2000 L single-use bioreactors of the type now used for viral vectors may be needed for allogeneic applications to achieve the required cell volumes.

"Suspension processes for allogeneic manufacturing have been established for some time, so there has been more work adapting processes for these needs than there has been for vector production," says Bulpin. Closed, automated technology platforms will be critical in the future, he says.

Autologous therapy development will not be one size fits all, says Krallis, who emphasizes the need for "mass customization," which she defines as "automating processes while remaining flexible from the clinical-to-commercial phase and adapting to the quality of the raw material." Lonza launched its closed, automated Cocoon platform (acquired via its purchase of Octane Biotech in 2018), which aims to help developers achieve this goal and is currently being used by Sheba Medical Center to produce autologous therapies (8).

Automation and digitization

Although most biopharmaceutical companies are adopting automation, cell and gene therapies pose challenges, says Bulpin. "Unlike monoclonal antibodies that utilize robust and predictable immortalized cell lines, CAR-T therapy requires the patient's own cells for further processing. Incoming cell composition from patient to patient is exceedingly variable. Automation and process control for CAR-T manufacturing will require a high degree of flexibility for variable cell inputs while also providing robust and predictive processing," Bulpin says.

Data management will also be crucial for autologous manufacturing, which will require patient tracking to ensure that the product makes its way back to the intended recipient. "It is also extremely important, given that many of these patients have not responded to chemotherapy and radiation therapy, that the manufacturing process be short and patient scheduling seamless," Bulpin says.

As he notes, the typical CAR-T manufacturing process can take anywhere from 20–30 days, with a significant portion of this time dedicated to release testing. Bulpin suggests that using in-line sensors for real-time quality control release testing could improve overall efficiency.

"To support this new type of manufacturing, we are going to need to replace as many manual processes as possible with closed and automated processes, so the labs will look very different as a result," Krallis says. In addition, she sees the need for a new digital approach to managing manufacturing systems. "Especially as we increase the number of patients treated per week with autologous cell and gene therapies, it is key to have the right data-management systems in your manufacturing setup to track and trace all patient material in real-time, before, during, and after manufacturing," she says.

Vanek agrees that digitalizing the overall process will be crucial to development of personalized medicine. "If you're translating from a clinic and you have a therapeutic that's progressing through clinical trials, there is a need for better data management and integration. Even at the unit operation level or the individual step of a larger process, just being able to connect data in a cohesive fashion is crucial," he says.

Digitalizing to improve manufacturing

Although many pharmaceutical companies are at a very early stage of digitalization, Vanek believes that capabilities can be adopted sequentially. The first step would involve connecting data with batch records and standard operating procedures (SOPs) so that the information becomes part of the manufacturing record. GE launched a platform called Chronicle in May 2019 (9) to enable e-notebook and e-SOP connection in a more streamlined way, he says.

[Krallis] believes that contract development and manufacturing organizations (CDMOs) can offer developers a way to control operating and capital costs, allowing them to focus on pipeline development.

"Entering data incorrectly at the production stage poses a very high risk to the manufacturing process, particularly for autologous therapies," he says. "So, our goal is to get the devices used across the process, independent of vendor, to have a consistent way of reporting out data and having data available to operators, to the quality assurance and regulatory affairs teams that are ultimately responsible for the quality of that product."

But he acknowledges that this is only the first level of integration. Data must flow from the patient through the manufacturing process and then back to the patient, and all the elements of the complex supply chain must be coordinated, he explains, so the second level of digital integration will connect digital patient records, the materials flowing in, as well as the production process into one manufacturing workflow.

"Ultimately, you want to escalate that integration to the point where it's part of a manufacturing execution system (MES), to start to schedule, coordinate, and orchestrate all the moving parts. This will require a much more sophisticated capability than the industry has today," Vanek says.

Facing challenges

Beyond digitization and automation, developers face a number of other challenges as they scale-up cell and gene therapies. One concern that Krallis notes is requirements for and availability of the complex raw materials (e.g., plasmids and lentivirus) required for manufacturing. In addition, she says, as the field evolves, developers must be careful about investing too-much too-soon in technologies that may soon be outdated, before they recover their capital expenditures, she says.

Ultimately, she says, developers face reimbursement challenges and the need to balance cost effectiveness in the scaled-up process with demands to reduce drug cost to patients. She believes that contract development and manufacturing organizations (CDMOs) can offer developers a way to control operating and capital costs, allowing them to focus on pipeline development.

CDMOs may have an advantage in being able to scale up or down, to adapt to changes in demand.

Bulpin sees the shift toward personalized, point-of-care medicine as a challenge for the delivery of finished therapies. Another hurdle is the long timeline from development through manufacturing, he says.

As more companies get involved in personalized medicine development, all stakeholders including operating companies, CDMOs, technology vendors, and research organizations are forming alliances to stay ahead of challenges and share different perspectives. One example is the Centre for Advanced Therapeutic Cell Technologies in Toronto, Canada, whose members include GE Healthcare and the NJII Cell and Gene Therapy Development Center, which works with Pall Corp.

The dynamics of collaborations in this field may differ from those in traditional biopharmaceutical development. One reason is the complexity of the supply chain, especially for autologous therapies, because the starting material is the patient's own cells, says Bulpin. "Closed and automated systems offer the potential for manufacturing sites to be located closer to the patient, regionally or even at the hospital. In this context, CDMOs may require satellite facilities, or academic medical centers may take on more of a CDMO role," he says.

Another difference from traditional biopharma is the fact that many of the therapies originated from research and discovery conducted by the doctors and academics at hospitals and research institutes, says Krallis. "Institutes can manufacture therapies for clinical trials but most of them don't have the expertise or the capacity to make product at commercial scale. Instead, the therapies get spun off to new companies and are usually tech-transferred to a CDMO," she says, noting that CDMOs may have an advantage in being able to scale up or down, to adapt to changes in demand.

"People have succeeded with therapeutic production at small scale, but we don't have industrial experience yet. All stakeholder groups must come together to share experiences and identify ways to retire risk, reduce costs, keep up with regulatory pace, and make safe and effective products available to patients who need them," Vanek says. "The pace of change and approvals is faster in this sector than we've ever seen before. Everyone is figuring this out as we go," he says.

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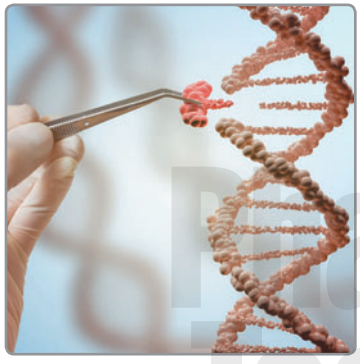
Gene-Editing Techniques Target New Applications

The Editors of *Pharmaceutical Technology*



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Industry experts discuss the role of gene-editing techniques in regenerative medicine and cell-line development.

Gene-editing methods such as clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 are used for disease research; clinical studies using the method are ongoing. A growing use of CRISPR-Cas9 and other gene-editing techniques to modify the genetic makeup of mammalian-based cells, such as Chinese hamster ovary (CHO) cells, is used for therapeutic antibody production.

To explore the role gene-editing techniques can play in regenerative medicine and cell-line development, *Pharmaceutical Technology* interviewed Lise Munsie, senior development manager at CCRM, a Toronto, Canada-based not-for-profit consortium that supports the development and commercialization of cell and gene therapies and regenerative medicine-based technologies, and Kevin Gamber, vice-president of Canopy Biosciences, a St. Louis, MO-based life-sciences company that offers tools and services for gene editing and bioprocessing applications.

Application of gene-editing tools

PharmTech: What is the most commonly used genome-editing tool today; how has this tool impacted the development of cell lines for use in therapeutic antibody production?

Munsie (CCRM): Although CCRM does not currently make therapeutic antibodies, the ability of CRISPR-Cas9 to easily manipulate the genome of antibody producing cells, such as CHO cells, to enhance antibody production would be game-changing. Scientists can easily alter genes they think are assisting the cells in antibody production, for instance, by manipulating genes that regulate the cell cycle or divert energy from other normal cellular processes towards antibody production. Prior to CRISPR-Cas9, this [manipulation] would have been too cumbersome to do in an efficient and relevant manner.

Gamber (Canopy Biosciences): CRISPR-Cas9 has taken the gene editing world by storm. It is more efficient and much easier to design and construct than previous gene-editing tools, such as zinc finger nucleases (ZFNs), [Transcription Activator-Like Effector Nucleases] TALENs, and meganucleases. For therapeutic antibody production, it

has been used both for site-specific integration of antibodies for bioproduction as well as to generate better host cells; the development of cells with increased yields, for example.

PharmTech: What other genome-editing tools are predominantly used today by the biopharmaceutical industry for cell-line engineering?

Munsie (CCRM): There are classic tools like ZFNs and TALENs. Scientists are increasingly making modified-Cas9 variants to make them more specific or efficient, and new enzymes that function in a manner similar to Cas are regularly being discovered.

Gamber (Canopy Biosciences): ZFNs are also used. ZFNs have a clearer intellectual property position than CRISPR. Additionally, stable cell lines are still being generated through standard transgenic techniques—transfection of a transgene followed by selection.

Pitfalls and potential

PharmTech: What are potential pitfalls or disadvantages of using a genome-editing tool to custom engineer CHO cells?

Gamber (Canopy Biosciences): The off-target effects generated by CRISPR-Cas9 have been well documented. Off-target effects occur when the gene editing tool makes unintended edits to other genes in addition to the target gene. Off-target editing is not species specific. Off-target effects can be largely mitigated through careful design of the reagents.

PharmTech: Will genome-editing technologies continue to play a significant role in customizing cell-line development, or are other technological tools expected to break through?

Munsie (CCRM): Gene editing is still in its infancy and will continue to be a major player in the cell-line engineering field for a long time to come.

Gamber (Canopy Biosciences): Gene editing via CRISPR-Cas9 will continue to be an extremely important tool for gene editing. Improvements on the technology are continuing to be made, as well as alternate systems being identified. Therapeutic use of CRISPR-Cas9 technology, such as Chimeric antigen receptor T cells as immunotherapy for cancer, will increase in use and hopefully become a powerful new approach to a wide variety of diseases.

PharmTech: What needs remain unmet in biologic drug engineering/development, and can genome-editing tools address these unmet needs?

Munsie (CCRM): Most regenerative medicines rely on autologous stem cell sources due to the immune response that occurs when allogeneic cells are introduced into a person. However, there is a lot of interest in using CRISPR-Cas9 to manipulate allogeneic cells and knock-out proteins that signal the immune system. These cells could then be used in multiple donors for many different therapies without the issue of rejection. Additionally, genome-editing can be used to knock-in genes. In the case of universal cells, it would be desirable to knock-in an exogenous gene that could be used as a kill switch in the event your regenerative medicine therapy had ill-intended effects. **PT**

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Pharma Contract Market Update

The Editors of *Pharmaceutical Technology*

SERJIOB74 - STOCK.ADOBE.COM

CMOs and CDMOs expanded their services and facilities in the summer of 2019.

Contract manufacturing organizations (CMOs) and contract development and manufacturing organizations (CDMOs) are constantly expanding, investing, and merging in order to provide their clients with the latest advancements and breakthroughs in services and technology. This article explores recent facility expansions and industry partnerships.

Facility acquisitions

In July 2019, Lonza Pharma & Biotech announced a binding contractual commitment for the purchase of a sterile drug product fill/finish facility from Novartis (1). The facility, located in Stein, Switzerland, will be the first sterile product finish/fill facility in Lonza's network for clinical supply and commercial launch.

The current good manufacturing practice (cGMP)-approved facility, which became operational in 2009, has been used for sterile clinical drug product manufacture; it comes equipped with classified cleanroom areas, office, lab, utilities, and storage space. According to a press statement, Lonza will continue to produce drug products for Novartis while providing additional capacity for pharma and biotech customers for development, testing, and manufacturing for parenteral medicines. The facility can produce liquid and lyophilized dosage forms in up to 200L volumes.

In June 2019, Catalent agreed to purchase Bristol-Myers Squibb's oral solid, biologics, and sterile product manufacturing and packaging facility in Anagni, Italy (2). The 19,300-m^2 facility, located 100 kilometers southeast of Rome, opened in 1966. The site is used to manufacture and package cardiovascular, neuroleptics, anticancer, metabolic and anti-inflammatory medicines, non-penicillin-based antibiotics, antivirals, and analgesics. Catalent reports it will continue to manufacture Bristol-Myers Squibb's current product portfolio at the site.

New facilities, expansions, and updates

Cambrex has revealed that it is expanding its solid form screening and crystallization process development facility in Edinburgh, Scotland to add supplementary laboratory space that will double the current footprint. In a July 30, 2019 press release, the company revealed that the expan-

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sion will enable recruitment of 40 more scientists, adding to the already employed 50, and will also allow for potential future growth (3). The expanded facility fit out is expected to commence late August 2019, and the company has set a target time for completion as the end of the year.

"This strategic expansion, the increase in headcount, and the investment in new equipment will enable us to serve more customers in the solid-state screening market," commented Mark Benger, Edinburgh site director, Cambrex, in a press release. "We have increasingly been asked by clients for additional services such as larger-scale crystallization, and we will now be able to provide these as well as adding greater efficiency and capacity at the Edinburgh site."

The expanded facility will feature additional instruments and reactors for large-scale crystallization studies and solid form screening capabilities. Furthermore, the company states that plans are in place for the installation of new ultra-high-performance liquid chromatography and gas chromatography instruments, as well as additional process analytical technology tools.

STA Pharmaceutical Co., Ltd., (WuXi STA), a subsidiary of WuXi AppTec, announced in July that its Analytical Service Unit (ASU) in Shanghai and its API process R&D and manufacturing facility in Changzhou passed FDA inspections (4). According to a July 23, 2019 press statement, the company has passed seven FDA inspections since 2013 and has produced branded drugs marketed in 95 countries. Its ASU gives clients access to analytical method development, validation, and testing services from preclinical to commercial, and its API process R&D and manufacturing facility produced a variety of new technology platforms such as spray dried dispersion, continuous processing, oligonucleotides, and peptides.

"It's a point of great pride that our quality systems allow us to be inspected at short notice by any applicable regulatory agency in the world. In this case, we received two separate inspection notices from FDA only seven days and five days in advance of the inspections, respectively. It's an endorsement of the real time monitoring and quality culture we run across all parts of the company," said Mei Hao, vice president of Quality at WuXi STA, in a press statement. "It's another key example of the rigorous nature of our global standard quality systems. It is also another milestone for our platform, and in our efforts to have geographically integrated capabilities for both drug product and drug substance."

Catalent is expanding the company's global spray drying capacity through an agreement with Sanofi Active Ingredient Solutions, which gives Catalent access to spray drying manufacturing equipment at Sanofi's Haverhill, United Kingdom facility (5). This agreement, announced on July 9, 2019, gives Catalent access to the Niro (GEA) PSD2 and PSD4 spray driers at the facility for customer projects. The facility includes clean area facilities for solvent and aqueous processing of potent or non-potent drug formulations, a secondary vacuum dryer, and integrated quality control and analytical capabilities. Catalent reports that the company can now offer spray drying solutions from early-phase development through commercial finished dose form manufacturing in Europe.

Earlier in 2019, Catalent announced a $40-million investment in its Winchester, KY facility, which includes commercial-scale spray drying with high-potent handling capabilities and other increases to the site's capacity.

In July 2019, Lonza completed a $15-million expansion of its oral solid-dose (OSD) development and manufacturing capabilities at its Tampa, FL site (6). The expanded site will integrate services across early-stage product development, clinical trial material manufacture, and commercialization.

A new product development and quality control laboratory area adds 13 processing suites. Two new commerical packaging suites feature low-humidity environments and serialization for tracking and tracing of commercial products.

New manufacturing suites and dedicated sampling and dispensing areas capable of handling highly potent compounds were also added. In addition, Lonza renovated the cGMP manufacturing cleanroom facility and 25,000 ft^2 of the existing cGMP OSD manufacturing cleanroom facility.

Lonza also announced an expansion of its Visp, Switzerland facility after the approval of an antibody-drug-conjugate (ADC) produced at the site. This is the third ADC approved from the bioconjugation facility, according to a July 24, 2019 press statement (7). The additional space will provide customers with launch and commercial manufacturing and will serve the early clinical phase market for bioconjugates.

The company is currently working on bringing bioconjugates to market, specifically developing and manufacturing expression systems with site-specific integration vectors to a simplified supply chain with the option of all elements under the same quality system. By 2020, all materials will be located at a single site through IbexTMSolutions and the highly-potent API facility.

"With 11 INDs completed, and now three out of five commercially available ADCs supported by our bioconjugation facility, we see the need to expand in readiness for the new wave of therapies our customers are developing," said Karen Fallen, head of Mammalian and Microbial Development and Manufacturing for Lonza, in a press statement. "Many bioconjugates are on expedited programs, and the existing expertise at the facility, combined with proximity to clinical and commercial manufacturing of antibody, linkers and payload, will reduce risk and increase speed on the path to market."

Fujifilm Irvine Scientific is planning to open a third manufacturing facility in Tilburg, The Netherlands. The new facility will support bioproduction and cell- and gene-therapy markets (8). The new facility, part of Fujifilm Manufactur-

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ing Europe's center, will support cGMP manufacturing of annual component-free, dry powder media, liquid media, and downstream bioprocessing liquid.

On June 20, 2019, CDMO Piramal Pharma Solutions announced the opening of a new wing at its Riverview, MI, site, into which the company has invested $10 million to upgrade (9). The new wing will produce high-potency APIs (HPAPIs) with low occupational exposure levels (OELs).

The upgrade includes a new quality control (QC)/analytical lab and two kilo-labs in addition to a doubling of the office space to support growth at the Riverview site. To date, "the Riverview site has had the containment capability and engineering controls to safely handle HPAPIs with OELs down to 1mcg/m^3," at scales ranging from grams to approximately 250 kilos, according to the company.

The new wing, with its two kilo-labs and QC/analytical lab, strengthens the company's position in this area. "The new wing is designed with the required engineering controls and containment solutions to handle HPAPIs with OELs <1mcg/m^3 and as low as ~20ng/m^3." Materials will primarily be produced in this new wing at kilo-lab scales, and significant amounts of <5 kilos can also be produced.

Partnerships

In July 2019, Catalent Biologics announced that it has entered into a long-term strategic agreement to develop and manufacture an AveXis gene therapy treatment for spinal muscular atrophy (SMA), Zolgensma (onasemnogene abeparvovec-xioi) (10).

Under the terms of the agreement, Novartis company, AveXis, will have dedicated manufacturing space at a new commercial manufacturing center near Baltimore–Washington International Airport, which has been established by Paragon Gene Therapy—a unit of Catalent Biologics. In addition, Paragon Gene Therapy will provide process development for the clinical supply of additional viral therapies within the AveXis pipeline.

Zolgensma is a gene therapy that has already been approved by the US FDA for the treatment of SMA and includes treatment of patients who are pre-symptomatic at diagnosis. The therapy works by replacing the defective or missing SMN1 gene, which halts disease progression, with a one-time intravenous infusion.

This agreement builds on Catalent's previous investments in the gene therapy area. In May 2019, the company purchased Paragon Bioservices. And in June 2019, Catalent announced that the Paragon Gene Therapy unit would purchase the vaccine manufacturing equipment and facility assets and assume the leases of two Novavax product development and manufacturing facilities in Gaithersburg, MD (11).

More than 100 Novavax manufacturing and quality employees will transfer to Paragon. In addition, the companies announced an agreement in which Paragon will provide process development and manufacturing services for some Novavax programs.

In the press statement, Novavax noted that the approximately $18 million sale will enable the company to focus on advancing two products, NanoFlu and ResVax, through clinical development and regulatory review.

"This alliance is a true win-win-win for Paragon, Novavax and our employees," said Stanley C. Erck, president and chief executive officer of Novavax, in the press statement. "This mutually beneficial transaction allows Paragon to quickly support the growth of its gene therapy development and manufacturing business and simultaneously offers Novavax a strategic and cost-effective approach to addressing its manufacturing needs into the future."

In more Paragon news, Amicus Therapeutics, Inc. and Paragon Gene Therapy entered into a strategic manufacturing agreement in July for clinical manufacturing capabilities and capacity for multiple active preclinical lysosomal disorder programs currently in development in collaboration with the University of Pennsylvania (Penn) (12).Penn will collaborate with Amicus throughout the process, and current research and development production related to active preclinical lysosomal disorder programs will be transferred to and developed at Paragon.

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Sales Contact: Bettina Berger
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Number of Employees: 101-250

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Business Unit Head: John Chiminski
Sales Contact: Will Downie
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Sales Contact: Joseph St. Laurent
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Number of Employees: 26-50

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Annual Revenues: $25-50 million

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Sales Contact: Patrick Depalma, Dir Bus Dev
Year Founded: 1998
Number of Employees: 501+
Annual Revenues: $250-500 million

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Biomanufacturing: Cell culture; Microbial fermentation; Microbial Manufacturing; Vaccines.
Commercial manufacturing: Active Pharmaceutical Ingredients (API) manufacturing - (cGMP, large molecules/biologics); Parenteral drug manufacturing (Injectables, etc.).
Formulation Development & Phase I/II Clinical Trial Materials (CTM): Active Pharmaceutical Ingredients (API) - large molecule/biologics; Injectable products development.
Packaging & logistics: Commercial packaging.

See our ad on page s41

Eurofins Lancaster Labs

2425 New Holland Pike
Lancaster, PA 17601 USA
Tel: 717-656-2300
Fax: 717-656-3772
Email: pha@eurofinsus.com
Website: www.eurofinslancasterlabs.com
Number of Employees: 501+

OUTSOURCING SERVICES

Analytical services: Bioanalytical testing; Chemistry & stability; Microbiology; Particle characterization; Product characterization.
Biomanufacturing: Cell culture.

Federal Equipment Co

8200 Bessemer Ave
Cleveland, OH 44127-1837 USA
Tel: 800-652-2466
Email: pharmaceutical@fedequip.com
Website: www.fedequip.com
Sales Contact: Adam Covitt
Year Founded: 1957

OUTSOURCING SERVICES

Consulting services: Project & sourcing management services.
Packaging & logistics: Clinical labels; Commercial packaging.

Fillab

11750 Fourth Ave
Montreal, Quebec H1E 3B3 Canada
Tel: 514-494-8286
Fax: 514-643-1518
Email: info@fillab.com
Website: www.fillab.com
Number of Employees: 26-50
Annual Revenues: $0-10 million

OUTSOURCING SERVICES

Packaging & logistics: Commercial packaging.

Gibraltar Labs

122 Fairfield Rd
Fairfield, NJ 07004 USA
Tel: 973-227-6882
Fax: 973-227-0812
Email: drinaldi@gibraltarlabsinc.com
Website: www.gibraltarlabsinc.com
Sales Contact: Danina Rinaldi
Year Founded: 1970
Number of Employees: 51-100
Annual Revenues: $10-25 million

OUTSOURCING SERVICES

Analytical services: Bioanalytical testing; Chemistry & stability; Microbiology.

Grand River Aseptic Mfg

140 Front Ave SW Ste 3
Grand Rapids, MI 49504-6426 USA
Tel: 616-218-3753
Email: info@grandriverasepticmfg.com
Website: www.grandriverasepticmfg.com
Business Unit Head: April Ladd, Mgr of Bus Dev
Sales Contact: Val Dittrich
Year Founded: 2011
Number of Employees: 101-250

OUTSOURCING SERVICES

Commercial manufacturing: Parenteral drug manufacturing (Injectables, etc.).
Formulation Development & Phase I/II Clinical Trial Materials (CTM): Injectable products development.
Packaging & logistics: Commercial packaging.

Green Ridge Consulting

376 SW Bluff Dr Ste 6
Bend, OR 97702-1399 USA
Tel: 541-385-4748
Fax: 541-610-1938
Email: leah@greenridgeconsulting.com
Website: www.greenridgeconsulting.com
Sales Contact: Leah Appel, Mng Partner
Year Founded: 2007
Number of Employees: 1-25
Annual Revenues: $0-10 million

OUTSOURCING SERVICES

Commercial manufacturing: Solid dose manufacturing.
Formulation Development & Phase I/II Clinical Trial Materials (CTM): Solid dose, semi-solids & liquids development.

Jubilant HollisterStier

3525 N Regal St
Spokane, WA 99207 USA
Tel: 509-489-5656/800-655-5329
Email: info@jublhs.com
Website: www.jublhs.com
Business Unit Head: Amit Arora, Pres
Sales Contact: Mark Sassler
Year Founded: 1921
Number of Employees: 501+

OUTSOURCING SERVICES

Commercial manufacturing: Parenteral drug manufacturing (Injectables, etc.); Semi-solids & liquid manufacturing; Specialty dosage forms (inhalation/nasal, transdermal, other).

See our ad on page s52

Lonza

Muenchensteinerstrasse 38
Basel, CH-4002 Switzerland
Tel: +41-61-316-81-11
Fax: +41-61-316-91-11
Email: contact@lonza.com
Number of Employees: 501+
Annual Revenues: $500 million+

OUTSOURCING SERVICES

Analytical services: Bioanalytical testing; Chemistry & stability; Microbiology; Particle characterization; Product characterization.
API and advanced intermediates (cGMP, small molecule) manufacturing capabilities: Biocatalytsis; Borane chemistry; Bromine chemistry/bromination; Chemocatalysis; Cryogenics (low-temperature reactions); Fluorination; Hydrazine chemistry; Nitration; Phosgenation.
Biomanufacturing: Cell culture; Microbial fermentation; Microbial Manufacturing; Nucleic acids; Stem cell production; Vaccines.
Commercial manufacturing: Active Pharmaceutical Ingredients (API) and advanced intermediates manufacturing (cGMP, small molecule); Active Pharmaceutical Ingredients (API) manufacturing - (cGMP, large molecules/ biologics); High-potency or high-containment manufacturing (finished drug product); Ingredient processing (milling, coating, etc.); Parenteral drug manufacturing (Injectables, etc.); Semi-solids & liquid manufacturing; Solid dose manufacturing; Specialty dosage forms (inhalation/nasal, transdermal, other).

Formulation Development & Phase I/II Clinical Trial Materials (CTM): Active Pharmaceutical Ingredients (API) - large molecule/biologics; Active Pharmaceutical Ingredients (API) - small molecule; Injectable products development; Other delivery forms (transdermal, inhalable...); Solid dose, semi-solids & liquids development.
Packaging & logistics: Clinical packaging & distribution; Commercial packaging.

See our ad on page s17

Metrics Contract Services

1240 Sugg Pkwy
Greenville, NC 27834 USA
Tel: 252-752-3800
Fax: 252-758-8522
Email: marketing@metricsinc.com
Website: www.metricscontractservices.com
Year Founded: 1994
Number of Employees: 251-500

OUTSOURCING SERVICES

Analytical services: Chemistry & stability; Microbiology; Particle characterization.
Commercial manufacturing: High-potency or high-containment manufacturing (finished drug product); Ingredient processing (milling, coating, etc.); Semi-solids & liquid manufacturing; Solid dose manufacturing; Specialty dosage forms (inhalation/nasal, transdermal, other).
Formulation Development & Phase I/II Clinical Trial Materials (CTM): Active Pharmaceutical Ingredients (API) - small molecule; Solid dose, semi-solids & liquids development.

Micro Measurement Labs

1300 S Wolf Rd
Wheeling, IL 60090-6444 USA
Tel: 847-459-6540
Fax: 847-459-3088
Email: customerservice@mmlabs.com
Website: www.mmlabs.com

OUTSOURCING SERVICES

Analytical services: Particle characterization.

Micromeritics

4356 Communications Dr
Norcross, GA 30093-2901 USA
Tel: 770-662-3630
Fax: 678-348-7565
Email: ussales@micromeritics.com
Website: www.micromeritics.com
www.particletesting.com
Business Unit Head: Greg Thiele, Gen Mgr
Sales Contact: Bryan Shaw
Year Founded: 1962
Number of Employees: 251-500
Annual Revenues: $50-100 million

OUTSOURCING SERVICES

Analytical services: Bioanalytical testing; Chemistry & stability; Particle characterization; Product characterization.

Nelson Labs

6280 S Redwood Rd
Salt Lake City, UT 84123 USA
Tel: 801-290-7500/800-826-2088
Fax: 801-290-7998
Email: sales@nelsonlabs.com
Website: www.nelsonlabs.com
Business Unit Head: Jeffery Nelson, Pres
Sales Contact: Todd Sierer
Year Founded: 1985
Number of Employees: 500+

OUTSOURCING SERVICES

Analytical services: Chemistry & stability; Microbiology.
Consulting services: Regulatory, validation, IT, and QA/QC services.

O'Neal

10 Falcon Crest Dr
Greenville, SC 29607 USA
Tel: 864-298-2000
Fax: 864-298-6350
Email: info@onealinc.com
Website: www.onealinc.com
Business Unit Head: Brian Gallagher, VP
Year Founded: 1975
Number of Employees: 101-250
Annual Revenues: $100-250 million

OUTSOURCING SERVICES

Consulting services: Project & sourcing management services.

Pace Analytical Life Sciences LLC

1311 Helmo Ave N
Oakdale, MN 55128 USA
Tel: 651-738-2728
Email: lifesciences@pacelabs.com
Website: www.pacelifesciences.com
Number of Employees: 251-500
Annual Revenues: $50-100 million

OUTSOURCING SERVICES

Analytical services: Chemistry & stability; Microbiology.
Formulation Development & Phase I/II Clinical Trial Materials (CTM): Active Pharmaceutical Ingredients (API) - large molecule/biologics; Active Pharmaceutical Ingredients (API) - small molecule; Injectable products development; Other delivery forms (transdermal, inhalable...); Solid dose, semi-solids & liquids development.

Particle Technology Labs Ltd

555 Rogers St Ste 4
Downers Grove, IL 60515-3776 USA
Tel: 630-969-2703
Fax: 630-969-2745
Email: sales@particletechlabs.com
Website: www.particletechlabs.com

OUTSOURCING SERVICES

Analytical services: Particle characterization; Product characterization.
Consulting services: Regulatory, validation, IT, and QA/QC services.

Pfizer CentreOne

235 E 42nd St
New York, NY 10017-5703 USA
Tel: 224-212-2267
Website: www.pfizercentreone.com
Business Unit Head: Karen Blair, VP Gen Mgr
Year Founded: 1988
Number of Employees: 501+
Annual Revenues: $250-500 million

OUTSOURCING SERVICES

Commercial manufacturing: Parenteral drug manufacturing (Injectables, etc.).
Packaging & logistics: Commercial packaging.

Phoenix Equipment Corp

333 Broad St Ste C
Red Bank, NJ 07701-2178 USA
Tel: 732-442-6990
Fax: 732-442-0036
Email: jesse@phxequip.com
Website: www.phxequip.com
Number of Employees: 1-25

OUTSOURCING SERVICES

Consulting services: Equipment Services; Investment Recovery.

Promed Pharma

15600 Medina Rd
Plymouth, MN 55447 USA
Tel: 763-331-3800
Email: info@promedpharmallc.com
Website: www.promedpharmallc.com
Business Unit Head: Pete Mangan, Pres
Sales Contact: James Arps
Year Founded: 2006
Number of Employees: 26-50
Annual Revenues: $10-25 million

OUTSOURCING SERVICES

Analytical services: Product characterization.
Commercial manufacturing: Specialty dosage forms (inhalation/nasal, transdermal, other).
Formulation Development & Phase I/II Clinical Trial Materials (CTM): Other delivery forms (transdermal, inhalable...).

Pyramid Laboratories

3598 Cadillac Ave
Costa Mesa, CA 92626 USA
Tel: 714-435-9800
Fax: 714-435-9585
Email: info@pyramidlabs.com
Website: www.pyramidlabs.com
Business Unit Head: Medhat Gorgy, Pres
Sales Contact: Pao-Li Wang, Ph.D.,
Year Founded: 1988
Number of Employees: 51-100
Annual Revenues: $10-25 million

OUTSOURCING SERVICES

Analytical services: Chemistry & stability.
Commercial manufacturing: Parenteral drug manufacturing (Injectables, etc.).
Formulation Development & Phase I/II Clinical Trial Materials (CTM): Injectable products development.

QPharma

22 South St
Morristown, NJ 07960 USA
Tel: 973-656-0011/888-742-7620
Fax: 973-656-0408
Email: info@qpharmacorp.com
Website: www.qpharmacorp.com
Business Unit Head: Patrick P. Den Boer, Pres & CEO
Sales Contact: John Cunningham
Year Founded: 1994
Number of Employees: 101-250

OUTSOURCING SERVICES

Consulting services: Project & sourcing management services; Regulatory, validation, IT, and QA/QC services.

Reed-Lane

359 Newark-Pompton Tpke
Wayne, NJ 07470 USA
Tel: 973-709-1090/877-290-1090
Fax: 973-709-1091
Email: jluke@reedlane.com
Website: www.reedlane.com
Sales Contact: Joe Luke
Year Founded: 1959
Number of Employees: 101-250
Annual Revenues: $25-50 million

OUTSOURCING SERVICES

Packaging & logistics: Commercial packaging.

Regis Technologies

8210 Austin Ave
Morton Grove, IL 60053 USA
Tel: 847-967-6000
Fax: 847-967-5876
Email: sales@registech.com
Website: www.registech.com
Business Unit Head: Andy Miles, Dir Bus Dev
Sales Contact: Andy Miles
Year Founded: 1956
Number of Employees: 51-100
Annual Revenues: $10-25 million

OUTSOURCING SERVICES

Analytical services: Chemistry & stability.
API and advanced intermediates (cGMP, small molecule) manufacturing capabilities: Acetylenic chemistry; Acid chlorides; Acylation; Amidation; Amino acids and analogs; Asymmetric synthesis or chiral chemistry; Bromine chemistry/bromination; Cryogenics (low-temperature reactions); Heterocyclic chemistry; Nitration; Organometallic chemistry; Phosgenation; Sulfonation.
Commercial manufacturing: Active Pharmaceutical Ingredients (API) and advanced intermediates manufacturing (cGMP, small molecule).
Formulation Development & Phase I/II Clinical Trial Materials (CTM): Active Pharmaceutical Ingredients (API) - small molecule.

Rottendorf Pharma

875 N Michigan Ave
Chicago, IL 60611-1803 USA
Tel: 312-794-7836
Website: www.rottendorf.com
Business Unit Head: Dr. Stephan Fleck, CEO
Sales Contact: gema.moreno_cobo@rottendorf.com
Year Founded: 1929
Number of Employees: 501+
Annual Revenues: $100-250 million

OUTSOURCING SERVICES

Analytical services: Chemistry & stability; Product characterization.
Commercial manufacturing: Solid dose manufacturing.
Packaging & logistics: Commercial packaging.

Sartorius Stedim Biotech

565 Johnson Ave
Bohemia, NY 11716 USA
Tel: 631-254-4249
Email: leadsna@sartorius.com
Website: www.sartorius.com
Number of Employees: 500+
Annual Revenues: $500 million+

OUTSOURCING SERVICES

Analytical services: Bioanalytical testing; Microbiology; Particle characterization; Product characterization.
Biomanufacturing: Cell culture; Microbial fermentation; Microbial Manufacturing; Vaccines.
Consulting services: Equipment Services; Regulatory, validation, IT, and QA/QC services.

Senopsys

800 W Cummings Park Ste 1500
Woburn, MA 01801-6353 USA
Tel: 781-935-7450
Email: david.tisi@senopsys.com
Website: www.senopsys.com
Year Founded: 2006

OUTSOURCING SERVICES

Analytical services: Product characterization.

Spectrum Chemical Mfg Corp

769 Jersey Ave
New Brunswick, NJ 08901-3605 USA
Tel: 310-516-8000/800-772-8786
Fax: 800-525-2299
Email: marketing@spectrumchemical.com
Website: www.spectrumchemical.com
Business Unit Head: Mark Hurd, Gen Mgr
Sales Contact: Steve Minton
Year Founded: 1971

OUTSOURCING SERVICES

Analytical services: Product characterization.
API and advanced intermediates (cGMP, small molecule) manufacturing capabilities: Acetylenic chemistry; Acylation; Amidation; Amino acids and analogs; Asymmetric synthesis or chiral chemistry; Chemocatalysis; Cyanide chemistry; Fluorination; Heterocyclic chemistry; Hydrazine chemistry; Nitration; Organometallic chemistry; Phosgenation; Sulfonation.
Commercial manufacturing: Active Pharmaceutical Ingredients (API) and advanced intermediates manufacturing (cGMP, small molecule); Active Pharmaceutical Ingredients (API) manufacturing - (cGMP, large molecules/biologics).
Consulting services: Project & sourcing management services; Regulatory, validation, IT, and QA/QC services.
Formulation Development & Phase I/II Clinical Trial Materials (CTM): Active Pharmaceutical Ingredients (API) - large molecule/biologics; Active Pharmaceutical Ingredients (API) - small molecule.

University of Iowa Pharmaceuticals

College of Pharmacy G-20 115 S Grand Ave
Iowa City, IA 52242 USA
Tel: 319-335-8674
Fax: 319-335-9418
Email: randhall-yeates@uiowa.edu
Website: www.uip.pharmacy.uiowa.edu
Business Unit Head: Randy Yeates, Dir Bus Dev
Sales Contact: Randy Yeates
Year Founded: 1974

OUTSOURCING SERVICES

Analytical services: Chemistry & stability.
Commercial manufacturing: High-potency or high-containment manufacturing (finished drug product); Parenteral drug manufacturing (Injectables, etc.); Semi-solids & liquid manufacturing; Solid dose manufacturing.
Formulation Development & Phase I/II Clinical Trial Materials (CTM): Injectable products development; Solid dose, semi-solids & liquids development.

Velesco Pharma

28036 Oakland Oaks Ct
Wixom, MI 48393 USA
Tel: 734-545-0696
Email: gerry.cox@velescopharma.com
Website: www.velescopharma.com
Number of Employees: 1-25
Annual Revenues: $0-10 million

OUTSOURCING SERVICES

Analytical services: Chemistry & stability.
Formulation Development & Phase I/II Clinical Trial Materials (CTM): Active Pharmaceutical Ingredients (API) - small molecule; Solid dose, semi-solids & liquids development.
Packaging & logistics: Clinical packaging & distribution.

Veltek Associates

15 Lee Blvd
Malvern, PA 19355 USA
Tel: 610-644-8335
Fax: 610-644-8336
Email: vai@sterile.com
Website: www.sterile.com
Year Founded: 1981
Number of Employees: 101-250

OUTSOURCING SERVICES

Consulting services: Regulatory, validation, IT, and QA/QC services.

Wickham Labs Ltd

Hoeford Point, Barwell Lane
Gosport, PO13 0AU United Kingdom
Tel: +44-01329-226600
Email: mail@wickhamlabs.co.uk
Website: www.wickhamlabs.co.uk
Business Unit Head: Dr John McKenzie
Sales Contact: Rob Dalby
Number of Employees: 101-250
Annual Revenues: $0-10 million

OUTSOURCING SERVICES

Analytical services: Microbiology.
Consulting services: Regulatory, validation, IT, and QA/QC services.

Ad Index

At Contec, we don't just make cleanroom products – we've transformed the cleanroom industry. We don't just follow best practices, we created them. So know that when you clean with Contec, you're not just cleaning – you're putting up the industry's strongest defense against contaminants.

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